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<p>(54) Title: CEPHEM DERIVATIVES AND A METHOD FOR PRODUCING THE COMPOUNDS AND AN ANTIBACTERIAL COMPOSITION CONTAINING THE COMPOUNDS</p>			
<p style="text-align: right;">(I)</p>			
<p>(57) Abstract</p> <p>The present invention relates to novel cephem derivatives in which known phenyl oxazolidinone derivatives are chemically combined with cephem, a process for producing the cephem derivatives, and a pharmaceutical antibacterial composition containing the cephem derivatives. The structural formula of the cephem derivatives compounds is represented as in formula (I).</p>			

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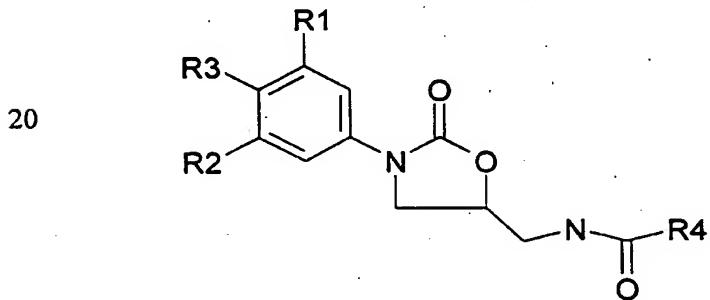
**CEPHEM DERIVATIVES AND A METHOD FOR
PRODUCING THE COMPOUNDS AND AN ANTIBACTERIAL
COMPOSITION CONTAINING THE COMPOUNDS**

5 FIELD OF THE INVENTION

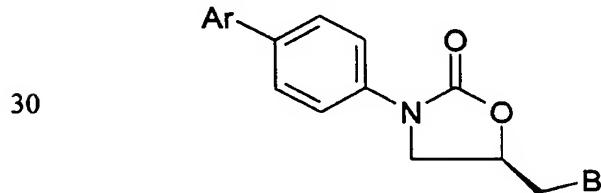
The present invention relates to novel cephem derivatives in which known phenyl oxazolidinone derivatives are chemically combined with cephem, a process for producing the cephem derivatives, and a pharmaceutical antibacterial composition containing the cephem derivatives.

BACKGROUND OF THE INVENTION

International Patent Publication No. WO 93/09103 discloses substituted aryl- and heteroaryl-phenyl oxazolidinones which may be useful as antibacterial agents. The structural formula is represented as follows:



25 US Patent No. 5,254,577 discloses aminomethyloxooxazolidinyl arylbenzen derivatives which can be used as antibacterial agents. The structural formula is represented as follows:



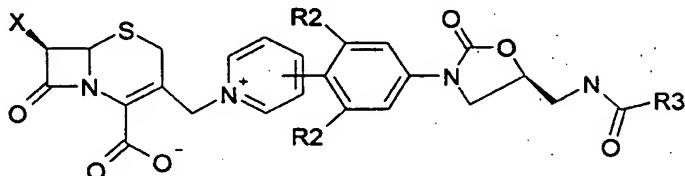
Some of pyridine-substituted phenyl oxazolidinone derivatives disclosed in the above patents are effective against Gram-positive bacteria such as *Staphylococcus aureus* and *Streptococcus pneumoniae*. However, they are not active against Gram-negative bacteria such as *Escherichia coli*, *Klebsiella*, *Proteus*, and *Seratia marcescens*. Moreover, 5 they cannot be administered as an injection solution because their free amine forms are little soluble.

The inventors have intensively studied to develop new antibacterial agents which have effective and excellent activity against Gram-negative bacteria and Gram-positive bacteria, and which are soluble so that they can be used as an injection solution. As a 10 result, the structurally new compounds were produced by chemically reacting known antibacterial oxazolidinone compounds with cephem compounds. They were found to be potently active against Gram-negative bacteria as well as Gram-positive bacteria.

15 SUMMARY OF THE INVENTION

The present invention provides compounds of the formula I:

20

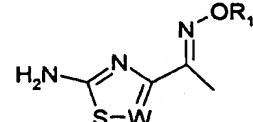
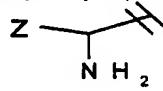


25

or pharmaceutically acceptable salts or hydrates thereof wherein

X is i) amine or protected amine, ii) $\text{Y}-\text{C}(=\text{O})-\text{N}-\text{R}$ in which Y is i) hydrogen, ii) $\text{C}_1\text{-C}_6$ lower alkyl optionally substituted with at least one selected from the group consisting of chlorine, fluorine, cyano, nitro, hydroxy, amino, $\text{C}_1\text{-C}_4$ alkylamino, $\text{C}_1\text{-C}_4$ dialkylamino, hydroxylamino, $\text{C}_1\text{-C}_4$ alkoxyamino, $\text{C}_1\text{-C}_4$ alkoxyimino, $\text{C}_1\text{-C}_4$ alkoxy, $\text{C}_1\text{-C}_4$ acyloxy, 30 $\text{C}_1\text{-C}_4$ alkylsulfonyl, $\text{C}_1\text{-C}_4$ alkylsulfenyl, $\text{C}_1\text{-C}_4$ alkylsulfinyl, $\text{C}_1\text{-C}_4$ alkylaminosulfonyl,

and carboxylic acid and inorganic cation salt thereof, iii) C_2 - C_6 alkenyl optionally substituted with at least one selected from the group consisting of chlorine, fluorine, cyano, nitro, hydroxy, amino, C_1 - C_4 alkylamino, C_1 - C_4 dialkylamino, hydroxylamino, C_1 - C_4 alkoxyamino, C_1 - C_4 alkoxyimino, C_1 - C_4 alkoxy, C_1 - C_4 acyloxy, C_1 - C_4 alkylsulfonyl, 5 C_1 - C_4 alkylsulfonyl, C_1 - C_4 alkylsulfinyl, C_1 - C_4 alkylaminosulfonyl, and carboxylic acid and inorganic cation salt thereof, iv) C_2 - C_6 alkynyl optionally substituted with at least one selected from the group consisting of chlorine, fluorine, cyano, nitro, hydroxy, amino, C_1 - C_4 alkylamino, C_1 - C_4 dialkylamino, hydroxylamino, C_1 - C_4 alkoxyamino, C_1 - C_4 alkoxyimino, C_1 - C_4 alkoxy, C_1 - C_4 acyloxy, C_1 - C_4 alkylsulfonyl, C_1 - C_4 alkylsulfonyl, C_1 - C_4 alkylaminosulfonyl, and carboxylic acid and inorganic cation salt thereof, 10 v) phenyl optionally substituted with at least one selected from the group consisting of chlorine, fluorine, cyano, nitro, hydroxy, amino, C_1 - C_4 alkylamino, C_1 - C_4 dialkylamino, hydroxylamino, C_1 - C_4 alkoxyamino, C_1 - C_4 alkoxyimino, C_1 - C_4 alkoxy, C_1 - C_4 acyloxy, C_1 - C_4 alkylsulfonyl, C_1 - C_4 alkylsulfinyl, C_1 - C_4 alkylaminosulfonyl, and carboxylic acid and inorganic cation salt thereof, 15 vi) R_4 -(CH_2) n -, in which n is an integer of 0 to 3, and R_4 is 2-thiophenyl, 2-furyl, 2-pyrolyl, 4-thiazolyl, 1,2,4-thiadiazol-3-yl, 2-oxazolyl, or 5- or 6- membered heterocyclic compound having from 1 to 4 atoms of O, S and N which are substituted with at least one selected from the group consisting of chlorine, fluorine, hydroxy, amino, C_1 - C_4 alkyl, C_1 - C_4 acylamino, C_1 - C_4 alkylsulfonylamino, C_1 - C_4 alkoxy, and C_1 - C_4 acyloxy, 20 vii) in which Z is hydrogen, or C_1 - C_6 lower alkyl, C_1 - C_6 alkenyl, C_2 - C_6 alkynyl, phenyl or heterocyclic compound optionally substituted with at least one selected from the group consisting of chlorine, fluorine, cyano, nitro, hydroxy, amino, C_1 - C_4 alkylamino, C_1 - C_4 dialkylamino, hydroxylamino, C_1 - C_4 alkoxyamino, C_1 - C_4 alkoxyimino, C_1 - C_4 alkoxy, C_1 - C_4 acyloxy, C_1 - C_4 alkylsulfonyl, C_1 - C_4 alkylsulfonyl, C_1 - C_4 alkylsulfinyl, C_1 - C_4 alkylaminosulfonyl, and carboxylic acid and inorganic cation salt thereof, and carbon having optical activity 25 can be optically pure (-), (+) or racemic forms, viii) in which W is CH or N , R_1 is hydrogen, or lower alkyl optionally substituted with carboxylic acid or 30



can be optically pure (-), (+) or racemic forms, viii) in which W is CH or N , R_1 is hydrogen, or lower alkyl optionally substituted with carboxylic acid or

inorganic cation salt thereof or protected carboxylic acid, and the alkoxyimino is a syn isomer;

R2 is hydrogen, fluorine, chlorine or methoxy and can be same or different;

5

R3 is hydrogen, or lower alkyl optionally substituted with carboxy or inorganic cation salt thereof, amino or alkoxy; and

provided that in the compounds of the formula I the phenyloxazolidinone is substituted
10 at 3 or 4 positions of pyridine.

DETAILED DESCRIPTION OF THE INVENTION

"Lower alkyl" herein means, unless indicated otherwise, straight or branched
15 alkyl having from 1 to 6 carbons and cycloalkyl having from 3 to 6 carbons. For example, C₁-C₆ alkyl include methyl, ethyl, propyl, isopropyl, butyl, t-butyl, pentyl, hexyl, and structural isomers thereof.

20 The R3 substituents are preferably hydrogen, methyl, difluoromethyl, dichloromethyl, hydroxymethyl, or methoxy and, most preferably, methyl.

25 The most preferred absolute configuration at C-5 of the oxazolidinone ring of the compounds according to the present invention is (S) under the Cahn-Ingold-Prelog nomenclature system. It is the (S)-enantiomer which possesses excellent activities against bacteria. The racemic mixture can be used in the same way and for the same purpose as the pure (S)-enantiomer. However, the difference is that twice as much reacemic material must be used to exhibit the same antibacterial activity as the pure (S)-enantiomer.

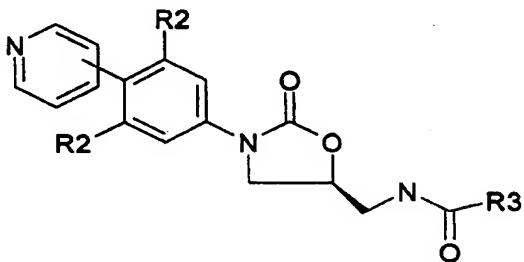
30 The pharmaceutically acceptable salts of the compounds I include inorganic cation salts such as alkaline metal salts (e.g., sodium or potassium) and alkaline earth metal salts (e.g., calcium or magnesium), inorganic salts such as hydrochloride,

hydrobromide, hydroiodide and sulfate, organic salts such as malate, lactate and tartarate, organic sulfonate such as benzenesulfonate, methanesulfonate and 4-tolunesulfonate, amino acid salts such as arginine, lysine and glycine, and amine salts such as trimethylamine, ammonia, triethylamine, pyridine, and picoline.

5

Examples of the substituents at C-3 position of cephem include the compounds of the formula II:

10



15

The specific examples of the compounds of the formula II are indicated in Table 1 below.

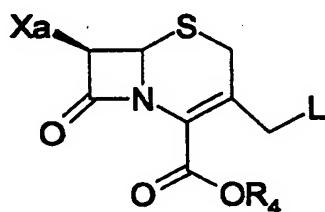
Table 1

NO.	Structural Formula	Compound Name	Reference for Synthesis
20	1	(S)-N-[[3-[3-fluoro-4-(4-pyridyl)phenyl]-2-oxo-5-oxazolidinyl]-methyl] acetamide	WO 93/09103
25	2	(S)-N-[[3-[3-fluoro-4-(3-pyridyl)phenyl]-2-oxo-5-oxazolidinyl]-methyl] acetamide	WO 93/09103

5	3		(S)-N-[(3-[4-(4-pyridyl)phenyl]-2-oxo-5-oxazolidinyl)methyl]acetamide	USP 5254577
10	4		(S)-N-[(3-[4-(3-pyridyl)phenyl]-2-oxo-5-oxazolidinyl)methyl]acetamide	USP 5254577
15	5		(S)-N-[(3-[3,5-difluoro-4-(4-pyridyl)phenyl]-2-oxo-5-oxazolidinyl)methyl]acetamide	WO 93/09103
20	6		(S)-N-[(3-[3,5-difluoro-4-(3-pyridyl)phenyl]-2-oxo-5-oxazolidinyl)methyl]acetamide	WO 93/09103

The compounds I or pharmaceutically acceptable salts thereof of the present invention can be produced by reacting the above compounds II with the compounds of the formula III:

25

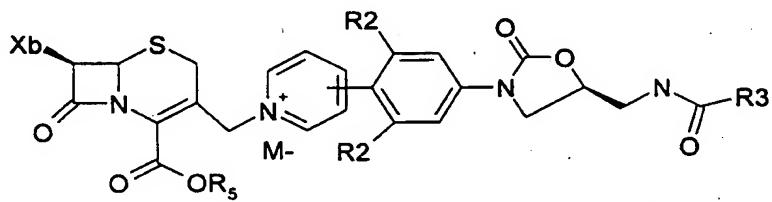


30

wherein Xa is the same as X defined above, except for amine and protected amine, R₄ is hydrogen or carboxylic acid-protecting group, and L is halogen atom or acetoxy. The halogen atom is chlorine, bromine or iodine. Bromine or iodine is especially preferable.

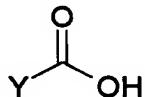
5 Alternatevely, the compounds I of the present invention can be produced by acylating the compounds of the formula V:

10



15

wherein Xb is amine or protected amine, R₅ is hydrogen or carboxylic acid-protecting group, M⁺ is anionic halogen such as chloride, bromide or iodide, or sulfonate, acetate, benzenesulfonate or citrate anions, with the compounds of the formula VI:



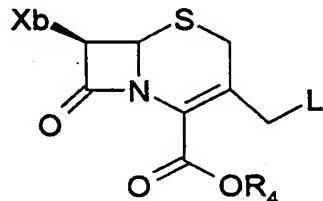
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wherein Y is the same as defined above. The most preferred anion M⁺ is chloride or bromide. In the absence of M⁺, the inner salt formed by monovalent anion of carboxylate and monovalent cation of pyridine is also preferable.

25

The compounds V can be prepared by C-3 reacting the compounds II with the compounds of the formula IV:

30



wherein X_b is amine or protected amine, R_4 is hydrogen or carboxylic acid-protecting group, and L is the same as defined above.

5 The reaction of the compounds II and the compounds III can be carried out at the temperature of from -30°C to 70°C. The preferred solvent is anhydrous solvent. The suitable organic solvents include lower nitrile such as acetonitrile and propionitrile, halogenated alkane such as chloroform, tetrachloromethane and dichloromethane, ether such as tetrahydrofuran and dioxane, amide such as N,N-dimethylformamide and N,N-dimethylacetamide, ester such as ethylacetate and methylacetate, ketone such as acetone, 10 methylethylketone and methylisobutylketone, sulfoxide such as dimethylsulfoxide, aromatic hydrocarbon such as benzene and toluene, and mixtures thereof.

15 Protecting groups which do not participate in the displacement reaction of the compounds II and III may be introduced to amine, carboxyl and alcohol groups of the compounds II and III. Examples of the amine-protecting group include formyl, acetyl, chloroacetyl, dichloroacetyl, t-butoxycarbonyl, benzyloxycarbonyl, triphenyl, benzyl, 4-methoxybenzyl, diphenylmethyl, triloweralkylsilyl and trimethylsilyl. The carboxyl-protecting groups include for example t-butyl, benzyl, 4-methoxybenzyl, benzyl, 4-nitrobenzyl, diphenylmethyl, methyl, 2,2,2-trichloroethyl, pivaloyloxymethyl, 20 triloweralkylsilyl and trimethylsilyl. Examples of the alcohol-protecting group include acetoxy, methoxymethyl, tetrahydrofuranyl, t-butyl, benzyl, and 4-methoxybenzyl.

25 Alternatively, amine, carboxyl and alcohol groups of the compounds II and III can be simultaneously protected by silylation. N,O-bis(trimethylsilyl)acetamide, N-methyl-N-(trimethylsilyl)acetamide, N,O-bis(trimethylsilyl)trifluoroacetamide, N-methyl-N-(trimethylsilyl)trifluoroacetamide and the like can be used as a silylating reagent. The silylating reagents are advantageous in that they make it possible to simultaneously protect amine, carboxyl and alcohol groups in an anhydrous solvent such as dichloromethane.

30

When L in the compounds IV is halogen atom such as bromine or iodine, the

compounds V can be obtained by reacting the compounds II with a silylating reagent such as N,O-bis(tri-loweralkylsilyl)acetamide or N,O-bis(tri-loweralkylsilyl)trifluoroacetamide in an anhydrous solvent such as dichloromethane or acetone at the temperature of from -30° to 60°C, followed by, if necessary, deprotecting, and 5 crystalizing into hydrochloride, hydroiodide or sulfate salts or chromatographing over silical gel, alumina, resin, and the like.

When L in the compounds IV is acetoxy, e.g., the compound IV is 7-amino-3-acetoxymethyl-3-cephem-4-carboxylic acid (7-ACA), the compounds V can be obtained 10 by simultaneously protecting amine and carboxyl groups with a silylating reagent such as N,O-bis(tri-loweralkylsilyl)acetamide, N,O-bis(tri-loweralkylsilyl)trifluoroacetamide or hexamethylsilazane(HMDS) and then converting acetoxymethyl into iodomethyl using iodotrimethylsilane.

15 The protection and deprotection of the functional groups can be conducted by a conventional method in the art, for example, "Protective groups in Organic Synthesis, 2nd edition" (Greene, T.W., etc., John Wiley & Sons, New York, 1991). The pharmaceutically acceptable salts of the compounds II and III are the same as mentioned 20 in the compounds I.

25 The compounds II as the substituents at C-3 position of cephem, for example, (S)-N-[[3-[3-fluoro-4-(4-pyridyl)phenyl]-2-oxo-5-oxazolidinyl]-methyl]acetamide, are known and can be synthesized by methods described in International Patent Publication No. WO 93/09103 and US Patent No. 5254577.

The compounds I of the present invention can be isolated and purified by conventional extraction, crystallization and column chromatography in the art.

30 The antibacterial composition containing the compounds I or pharmaceutically acceptable salts thereof as an active ingredient can be formulated into solid or liquid

using conventional techniques in the art. The pharmaceutical composition of the present invention can be primarily administered by intravenous or intramuscular injections. In addition, the composition of the present invention can be used in the forms of capsule, tablet, powder, suppository, and the like.

5

Examples of the solid form containing the compounds I include powder, tablet, capsule, suppository, cachet, and the like. The solid form can contain at least one of thickener, flavourant, sweetener, solubilizer, lubricant, suspending agent, binder, encapsulating agent, and the like. Examples of nonactive solid carrier include magnesium carbonate, magnesium stearate, talc, glucose, lactose, pectin, dextrin, starch, gelatin, wax, cocoa butter, and the like. The liquid formulation can be solution, suspension or emulsion. Examples of the carrier for the liquid form include water, mixture of water and propyleneglycol, mixture of water and polypropyleneglycol, and the like. Additionally, additives such as pigment, solubilizer, sweetener, stabilizer, thickener, and the like can be included in the liquid formulation.

10 The antibacterial composition of the present invention can be applied directly to human and animals. In addition, it can be used as food preservatives, agricultural chemicals, and the like. When the composition of the present invention is used in the treatment of human or animals against microbial infection, the injection or oral administration is preferable.

15 The administration amount of the compounds I depends on sexuality, age, weight and symptom of the patients to be treated, administration route, and the like. Generally, the daily dosage is in the range of 1 mg/kg and 1,000 mg/kg. The preferable daily dosage is between 100 mg/kg and 500 mg/kg.

20 The compounds I of the present invention have broad activity against Gram-positive bacteria such as *Streptococcus*, *Staphylococcus*, *Conellebacterium*, *Bacillus*, *Enterococci*, and the like, and Gram-negative bacteria such as *Escherichia coli*, *Klebsiella*, *Serratia marcescens*, *Salmonella*, *Proteus*, and the like. Particularly, the

compounds I are effective against strains which are resistant to known antibiotics such as vancomycin, β -lactam antibiotics, quinolones, and the like.

5 The compounds I of the present invention are greatly valuable in that they can be used as an injection because their water solubility is at least 10%. In comparison, the known compounds indicated in the above Table 1 are active in vitro against Gram-positive bacteria and drug-resistant strains but their free bases cannot be used as an injection because of low solubility.

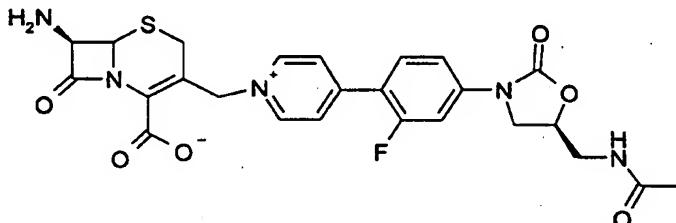
10 The invention will now be described with reference to the following illustrative Examples.

EXAMPLES

15 Reference Example 1

Preparation of 7 β -amino-3-[4-[2-fluoro-4-[5-[(S)-methylcarboxamidomethyl]-2-oxo-1,3-oxazol-3-yl]phenyl]-1-pyridiniomethyl]-3-cephem-4-carboxylate

20



25

3.8 ml of hexamethydisilazane was added to a suspension of 4.15 g of 7-aminocephalosporinic acid (7-ACA) in 50 ml of dichloromethane. 1 or 2 drops of iodotrimethylsilane were then added and the solution was refluxed with heat under nitrogen for 2 hours. 1.95 ml of chloromethylsilane was added and the solution was refluxed with heat for 30 minutes. The reaction mixture was cooled to 25°C. 8.35 ml of dimethylaniline was added and the solution was stirred for 30 minutes. 2.84 ml of iodotrimethylsilane was added under nitrogen and the solution was stirred at 20°C for 1.5 hours.

The resulting solution was mixed with the silylated pyridine derivative at 5°C, and the solution was stirred at 20°C for 2 hours. This silylated pyridine derivative was prepared as follows. (S)-N-[[3-[3-fluoro-4-(4-pyridyl)phenyl]-2-oxo-5-oxazolidinyl]-methyl]acetamide was used as a pyridine derivative and was synthesized according to the method described in international patent publication No. WO 93/09103. 5.65 g of the pyridine derivative was mixed with 30 ml of acetonitrile. The resulting solution was reacted with 9.57 ml of N,O-bis(trimethylsilyl)acetamide at 25°C for 2 hours to produce the silylated pyridine derivative. After the reaction was completed, a mixed solvent of 2.0 ml of methanol, 145 ml of acetone and 2.2 ml of water was slowly dropwise added so that deprotection took place. The reaction mixture was stirred at 5°C for 1 hour and the resulting solid was filtered under reduced pressure. The solid was washed with 3 x 20 ml of acetone and 2 x 30 ml of diethylether, and was dried under vaccum at 35°C to obtain 9.2 g of the title compound as hydroiodide salt. 5.0 g of the hydroiodide salt was mixed with 25 ml of water and 25 ml of acetone. The resuting solution was cooled to 10°C, and then 2 ml of concentrated hydrochloric acid was added to the solution and the reaction mixture was stirred for 30 minutes. 1 g of activated carbon was added to the solution, and the solution was then stirred for 30 minutes, and filtered. The filtrated was warmed to 25°C, and 25 ml of anhydrous ethanol and 100 ml of isopropylalcohol were slowly added to the solution. The reaction mixture was cooled to 5°C to yield precipitating crystals. 100 ml of isopropylalcohol was added to the solution and the resulting solution was stirred for 30 minutes. The solution was filtered under reduced pressure, washed with 3 x 20 ml of isopropylalcohol, 2 x 20 ml of acetone and 2 x 30 ml of diethylether, and dried under vacuum at 35°C to obtain 2.5 g of dihydrochloride salt of the title compound.

mp: 140°C to 169°C (decomposition).

NMR(400MHz, DMSO-d6):

9.08~9.11(2H,d,J=7.1 Hz), 8.43~8.46(2H,d,J=6.3 Hz), 8.32(1H,t),
7.96~8.02(1H,dd), 7.73~7.79(1H,dd), 7.60~7.63(1H,dd), 5.58~5.67(1H,dd),
5.17~5.23(3H,m), 4.82(1H,m), 4.20~4.24(1H,t), 3.84~3.88(1H,dd),
3.54~3.68(2H,ABq,J=18.2Hz), 3.44~3.47(2H,m), 1.84(3H,s)

Reference Example 2

Preparation of 2-(4-methoxybenzyloxy)acetic acid

1 g of ethylglycolate was dissolved in 10 ml of dimethylformamide. The solution
5 was cooled to 5°C. 0.38 g of 60% sodium hydride was added to the solution. The solution
was stirred for 10 minutes and was reacted with 1.3 ml of 4-methoxybenzylchloride at
25°C for 2 hours. The solution was extracted with 10 ml of water and 20 ml of
ethylacetate. The aqueous layer was extracted with 10 ml of ethylacetate, and the
collected organic layer was washed with 2 x 20 ml of water and 10 ml of brine, dried over
10 anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The
resulting oily residue was dissolved in 10 ml of anhydrous ethanol. The resulting solution
was mixed with an aqueous solution of 0.4 g of sodium hydroxide in 0.2 ml of distilled
water and the mixture was stirred for 3 hours. 10 ml of ethylacetate and 10 ml of water
were added to the solution, and the solution was then stirred for 30 minutes. After the
15 layers were separated, the organic layer was removed. 2N HCl was added to the aqueous
layer to adjust its pH to 1.0. The solution was extracted with 2 x 10 ml of
dichloromethane, dried over anhydrous sodium sulfate, filtered, and concentrated under
reduced pressure to obtain 1.3 g of the title compound.

mp: 52°C to 53°C

20 NMR(400MHz,DMSO-d6):

8.07(1H,s), 7.25(2H,m), 6.86(2H,m), 4.54(2H,s), 4.08(2H,s), 3.79(3H,s)

Reference Example 3

Preparation of 2-(4-methoxybenzyloxy)propanoic acid

25

Following the above Reference Example 2, but using ethyl(S)-(--)lactate as a
starting material, the title compound was prepared.

mp: 53°C to 54°C

NMR(400MHz,CDCl3):

30 7.29(2H,d), 6.89(2H,d), 4.62~4.48(2H,dd), 4.08(1H,q), 3.80(3H,s), 1.47(3H,d)

Reference Example 4

Preparation of 1H-1-imidazole acetic acid hydrochloride

5 g of imidazole was added to 50 ml of tetrahydrofuran and the resulting solution was cooled to -30°C. The cold solution was mixed with 3.2 g of 60% sodium hydride and the solution was stirred for 10 minutes. The solution was then reacted with 10.8 ml of tert-butyldibromoacetate at the same temperature for 1 hour. The solution was slowly warmed to 25°C and was stirred for 1 hour. The reaction mixture was extracted with 30 ml of water and 100 ml of ethyl acetate. The organic layer was dried over anhydrous sodium sulfate, filtered under reduced pressure, and concentrated under reduced pressure. Oily unpurified substances were mixed with 50 ml of ethyl ether and the mixture was stirred for 30 minutes. The resulting solid was isolated and dried to obtain 12.9 g of tert-butyl-1H-1-imidazole acetate. 2 g of tert-butyl-1H-1-imidazole acetate was dissolved in 20 ml of tetrahydrofuran and the resulting solution was reacted with 0.5 ml of 6N HCl at 55°C for 3 hours. The reaction mixture was concentrated under reduced pressure. The residue was added to 10 ml of ethylether, and the resulting solid was filtered and dried to obtain 1.0 g of the title compound.

mp: 208°C to 210°C

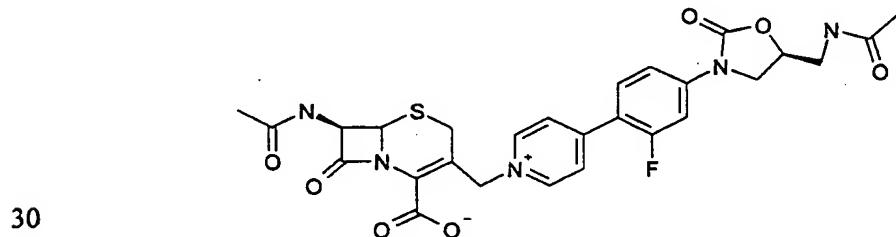
NMR(400MHz,DMSO-d6):

20 9.41(1H,s), 7.92(1H,s), 7.67(1H,s), 5.17(2H,s)

Example 1

Preparation of 7β-acetamido-3-[4-[2-fluoro-4-[5-[(S)-methylcarboxamidomethyl]-2-oxo-1,3-oxazol-3-yl]phenyl]-1-pyridiniomethyl]-3-cephem-4-carboxylate

25



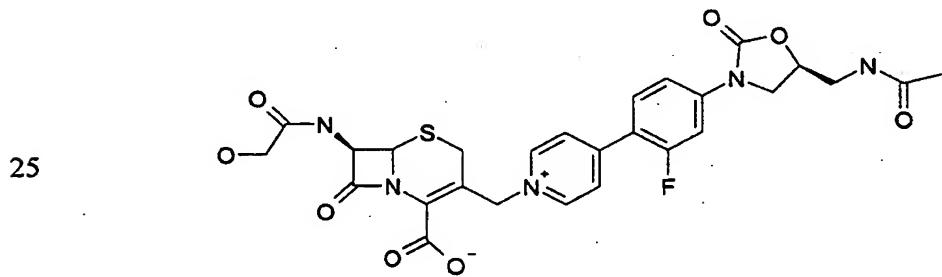
1.0 g of dihydrochloride salt of the title compound in the Reference Example 1 was dissolved in 20 ml of dichloromethane and 3 ml of methanol, and the resulting solution was cooled to 5°C. The cold solution was mixed with 0.74 ml of triethylamine, and the solution was stirred for 10 minutes. 0.7 ml of acetic anhydride was dropwise added to the solution for 10 minutes, and the solution was then stirred for 30 minutes. After the reaction was completed, the solvent was removed under reduced pressure. The residue was dissolved in an aqueous 50% ethanol, and the solution was concentrated under reduced pressure. The residue was chromatographed on silica gel using a mixed solvent of acetonitrile and water (4:1), concentrated under reduced pressure, and lyophilized to obtain 50 mg of the title compound.

10 NMR(400MHz, DMSO-d6):

15 9.49~9.52(2H,d), 8.75~8.78(1H,d), 8.37~8.40(2H,d), 8.27(1H,t),
7.93~7.98(1H,t), 7.73~7.78(1H,dd), 7.59~7.62(1H,dd),
5.54~5.59(1H,dd,J=3.8Hz), 5.03~5.70(2H,ABq,J=13.4Hz), 5.02~5.04(1H,d),
4.82(1H,m), 4.20~4.25(1H,t), 3.84~3.88(1H,dd), 3.08~3.58(2H,ABq,J=17.5Hz),
3.45~3.48(2H,m), 1.85(3H,s), 1.84(3H,s)

Example 2

20 Preparation of 7β-[2-hydroxy-acetamido]-3-[4-[2-fluoro-4-[5-[(S)-methylcarboxamidomethyl]-2-oxo-1,3-oxazol-3-yl]phenyl]-1-pyridiniomethyl]-3-cephem-4-carboxylate



30 1.0 g of dihydrochloride salt of the title compound in the Reference Example 1 was dissolved in 20 ml of dichloromethane and 3 ml of methanol and the resulting solution was cooled to 5°C. The cold solution was mixed with 0.74 ml of triethylamine

and the solution was then stirred for 10 minutes. 1 g of 2-(4-methoxybenzyloxy)acetic acid in the Reference Example 2 was dissolved in 10 ml of dichloromethane and the resulting solution was cooled to -30°C. The solution was reacted with 0.72 ml of triethylamine and 0.62 ml of pivaloylchloride for 1 hour and stirred at 25°C for 1 hour.

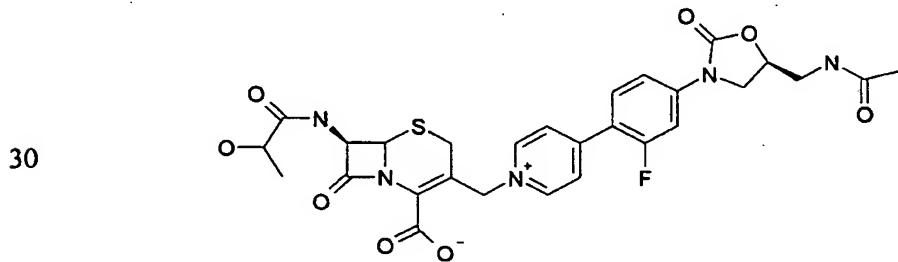
5 This acylating reagent was dropwise added to the solution for 10 minutes and the solution was then stirred for 1 hour. After the reaction was completed, the solvent was removed and the residue was mixed with 50 ml of ethyl acetate. The resulting solid was filtered and suspended in 10 ml of dichloromethane. The suspension was reacted with 1.0 ml of trifluoracetic acid and 0.5 ml of anisol at 25°C for 1 hour. 20 ml of isopropyl ether was added to the reaction mixture and the resulting solid was filtered. After the 10 unpurified solid was dissolved in an aqueous 50% ethanol, the pH of the solution was adjusted to 1.5 with 4N sulfuric acid and the resulting solution was concentrated under reduced pressure. The residue was chromatographed on silica gel by using a mixed solvent of acetonitrile and water (4:1), concentrated under reduced pressure and 15 lyophilized to obtain 50 mg of the title compound as sulfate salt.

NMR(400MHz,DMSO-d6):

9.14(2H,d,J=7.0Hz), 8.40(2H,d,J=6.3Hz), 8.20~8.40(2H,m), 7.94(1H,t),
 7.73~7.77(1H,dd), 7.59~7.62(1H,dd), 5.80~5.84(1H,dd),
 5.43~5.65(2H,ABq, J=14.5Hz), 5.56(1H,s), 5.20(1H,d), 4.82(1H,m), 4.22(1H,t),
 20 3.90(2H,s), 3.83~3.85(2H,m), 3.34~3.68(2H,ABq, J=18.2Hz), 3.44~3.47(2H,m),
 1.84(3H,s)

Example 3

Preparation of 7β-[2-hydroxy-2-methyl-acetamido]-3-[4-[2-fluoro-4-[5-[(S)-
 25 methylcarboxamido-methyl]-2-oxo-1,3-oxazol-3-yl]phenyl]-1-pyridiniomethyl]-3-
 cephem-4-carboxylate



1.0 g of dihydrochloride salt of the title compound in the Reference Example 1 was dissolved in 20 ml of dichloromethane and 3 ml of methanol and the resulting solution was cooled to 5°C. The cold solution was mixed with 0.74 ml of triethylamine and the solution was stirred for 10 minutes. 1.07 g of 2-(4-methoxybenzyloxy)propanoic acid in the Reference Example 3 was added to 10 ml of dichloromethane and the solution was cooled to -30°C. The cold solution was reacted with 0.62 ml of pivaloylchloride for 1 hour and was stirred at 25°C for 1 hour. This acylating reagent was dropwise added and the solution was stirred for 1 hour. 70 mg of the title compound was obtained by the same method in the Example 2.

10 NMR(400MHz,DMSO-d6):

9.01~9.06(2H,d), 8.42~8.45(2H,d), 8.20~8.40(2H,t), 7.95~8.00(1H,t),
 7.73~7.77(1H,dd), 7.60~7.62(1H,dd), 5.75~5.80(1H,dd), 5.45~5.64(2H,ABq),
 5.20(1H,d), 4.82(1H,m), 4.22(1H,t), 4.07~4.11(1H,m), 3.83~3.85(1H,m),
 3.35~3.69(2H, ABq), 3.44~3.47(2H,m), 1.85(3H,s)

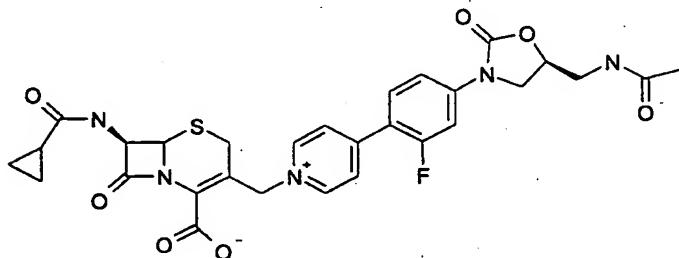
15

Example 4

Preparation of 7β-[2-cyclopropyl-acetamido]-3-[4-[2-fluoro-4-[5-[(S)-methylcarboxamidomethyl]-2-oxo-1,3-oxazol-3-yl]phenyl]-1-pyridiniomethyl]-3-cephem-4-carboxylate

20

25



0.1 g of dihydrochloride salt of the title compound in the Reference Example 1 was dissolved in 3.0 ml of dimethylformamide and 0.015 ml of cyclopropanecarboxylic acid was added to the solution. Subsequently, 0.03 ml of diethylcyanophosphate was added at 25°C and 0.08 ml of triethylamine was dropwise added for 5 minutes. The solution was stirred at the same temperature for 1 hour. 0.9 ml of isopropyl ether was

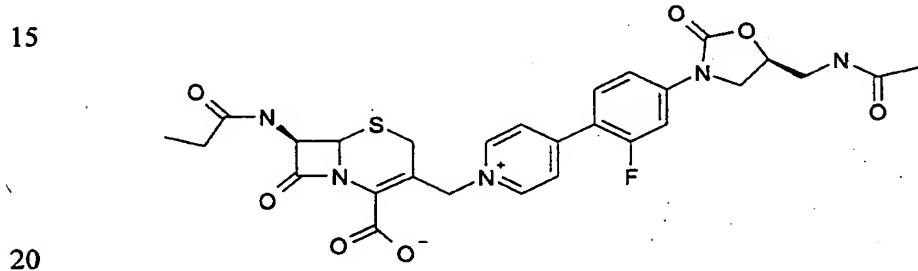
added to the solution and the resulting solid was filtered. The unpurified solid was purified as described in the Example 2 to obtain 10 mg of the title compound as sulfate salt.

NMR(400MHz,DMSO-d6):

5 9.06(3H,m), 8.43(2H,d), 8.24(1H,t), 7.96(1H,t), 7.74(1H,dd), 7.62(1H,dd),
 5.82(1H,dd), 5.45~5.65(2H,ABq), 5.15(1H,d), 5.27(1H,m), 4.83(1H,m),
 3.91(1H,m), 3.84(1H,m), 4.22(1H,t), 3.48~3.57(2H, Abq,J=18.2Hz),
 3.45(2H,m), 1.93(3H,s), 1.75(1H,m), 0.73(4H,m)

10 Example 5

Preparation of 7 β -[2-methyl-acetamido]-3-[4-[2-fluoro-4-[5-[(S)-methylcarboxamidomethyl]-2-oxo-1,3-oxazol-3-yl]phenyl]-1-pyridiniomethyl]-3-cephem-4-carboxylate



0.5 g of dihydrochloride salt of the title compound in the Reference Example 1 was dissolved in 15 ml of dichloromethane and 2.5 ml of methanol and the solution was cooled to 5°C. 0.37 ml of triethylamine was added and the solution was stirred for 10 minutes. 0.6 g of propionic acid was dissolved in 20 ml of dichloromethane and the solution was cooled to -30°C. The cold solution was reacted with 1.23 ml of triethylamine and 0.99 ml of pivaloylchloride for 1 hour and stirred at 25°C for 1 hour. This acylating reagent was dropwise added and the solution was stirred for 1 hour. After the reaction was completed, the solvent was removed and the residue was dissolved in 50% ethanol. The solution was purified as described in Example 2 to obtain 50 mg of the title compound as sulfate salt.

NMR(400MHz,DMSO-d6): 8.98(2H,d), 8.72(1H,d), 8.37(2H,d), 8.20(1H,t),

7.91(1H,t), 7.69(1H,dd), 7.54(1H,dd), 5.75(1H,dd), 5.50(2H,ABq),
 5.19(1H,d), 4.76(1H,m), 4.15(1H,t), 3.78(1H,dd),
 3.48~3.57(2H,ABq,J=18.1Hz), 3.42(2H,m), 2.10(2H,q), 1.77(3H,s),
 0.95(3H,t)

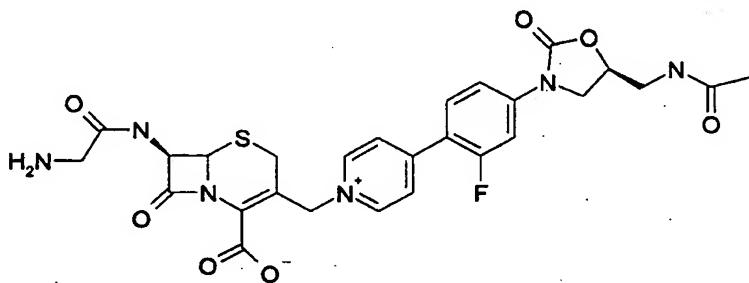
5

Example 6

Preparation of 7 β -[2-amino-acetamido]-3-[4-[2-fluoro-4-[5-[(S)-methylcarboxamidomethyl]-2-oxo-1,3-oxazol-3-yl]phenyl]-1-pyridiniomethyl]-3-cephem-4-carboxylate

10

15



0.3 g of dihydrochloride salt of the title compound in the Reference Example 1 was used as a starting material and 0.12 g of aminoacetylchloride hydrochloride was used as an acylating reagent. 30 mg of the title compound as hydrochloride salt was obtained by the same procedure in Example 1.

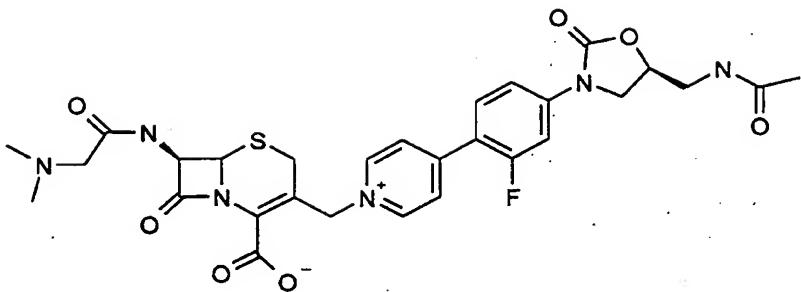
NMR(400MHz,DMSO-d6): 9.47(2H,d), 8.66(1H,d), 8.37(2H,d), 8.26(1H,t),
 7.95(1H,t), 7.73~7.77(1H,dd), 7.59~7.62(1H,dd), 5.60~5.70(1H,dd),
 5.05~5.20(2H,q), 5.56(1H,s), 4.91(1H,d), 4.82(1H,m), 4.22(1H,t),
 3.90(2H,s), 3.80~3.85(3H,m), 3.34~3.68(2H, ABq,J=18.2Hz),
 3.44~3.47(2H,m), 1.84(3H,s)

25

Example 7

Preparation of 7 β -[2-(N,N'-dimethylamino)-3-[4-[2-fluoro-4-[5-[(S)-methylcarboxamidomethyl]-2-oxo-1,3-oxazol-3-yl]phenyl]-1-pyridiniomethyl]-3-cephem-4-carboxylate

5



0.3 g of dihydrochloride salt of the title compound in the Reference Example 1
 10 was used as a starting material and 0.18 g of N,N'-dimethylaminochloride hydrochloride was used as an acylating reagent. 20 mg of the title compound as hydrochloride salt was obtained by the same procedure in Example 1.

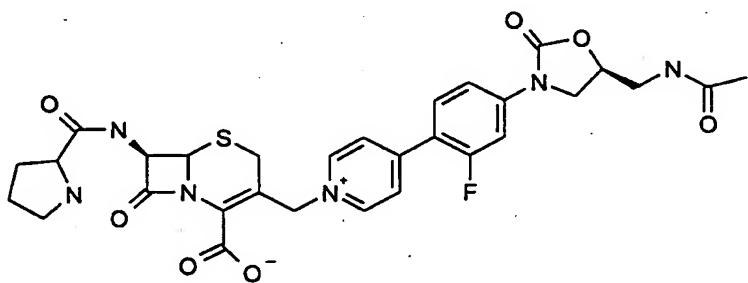
NMR(400MHz,DMSO-d6):

15 9.47(2H,d), 8.66(1H,d), 8.37(2H,d), 8.26(1H,t), 7.95(1H,t), 7.73~7.77(1H,dd),
 7.58~7.60(1H,dd), 5.90(1H,dd), 5.61~5.66(2H,m), 5.08~5.1(2H,m),
 4.83(1H,m), 4.22(1H,t), 4.00~4.10(2H,q), 3.83(1H,dd), 3.40~3.75(2H,ABq),
 3.08(6H,s), 1.84(3H,s)

Example 8

20 Preparation of 7β-[perhydro-2-pyrolyl-carboxamido]-3-[4-[2-fluoro-4-[5-[(S)-
 methylcarboxamido-methyl]-2-oxo-1,3-oxazol-3-yl]phenyl]-1-pyridiniomethyl]-3-
 cephem-4-carboxylate

25



30 0.5 g of N-(tert-butoxycarbonyl)-L-pyroline was dissolved in 5.0 ml of tetrahydrofuran. The solution was reacted with 0.38 g of 1-hydroxybenzotriazol and 0.51 g of 1,3-dicyclohexylcarbodiimide at 25°C for 1 hour. The resulting solid was filtered and

the parent liquid was concentrated to obtain an acylating ester reagent.

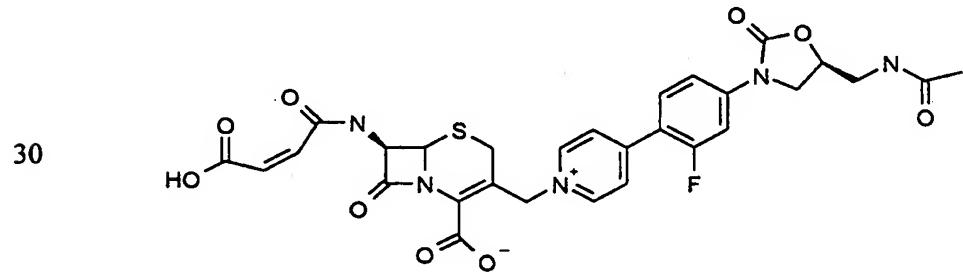
0.2 g of dihydrochloride salt of the title compound in the Reference Example 1 was dissolved in 5.0 ml of dimethylformamide and the solution was cooled to 5°C. The 5 0.1 ml of triethylamine was added and the solution was stirred for 10 minutes. The above prepared acylating reagent in 3.0 ml of dimethylformamide was dropwise added for 10 minutes. Then, the solution was stirred for 1 hour. After the reaction was completed, 10.0 ml of isopropylether was added to the solution and the resulting solid was filtered. The solid was suspended in 5.0 ml of dichloromethane and the suspension was reacted with 10 1.0 ml of trifluoroacetic acid at 25°C for 1 hour. After the reaction was completed, the solution was concentrated under reduced pressure. 10.0 ml of isopropylether was added and the resulting solid was filtered. The solid was dissolved in 50% ethanol and the solution was concentrated under reduced pressure. The residue was chromatographed with 15 silica gel using a mixed solvent of acetonitrile and water (4:1), concentrated under reduced pressure, and lyophilized to obtain 50 mg of the title compound as trifluoroacetate salt.

NMR(400MHz,DMSO-d6):

9.52(1H,d), 9.03(2H,d), 8.44(2H,d), 8.27(1H,t), 7.97(1H,t), 7.76(1H,dd),
7.62(1H,dd), 5.90(1H,dd), 5.45~5.63(2H,ABq), 5.25(1H,d), 4.84(1H,m),
20 4.22(2H,m), 3.84(1H,m), 3.63(1H,m), 3.40~3.60(2H,q), 3.20(2H,br),
2.52(1H,m), 1.94(2H,m), 1.85(3H,s), 1.20(2H,m)

Example 9

Preparation of 7β-[2-carboxy-(Z)-1-ethenyl-carboxamido]-3-[4-[2-fluoro-4-[5-[(S)-
25 methylcarboxamidomethyl]-2-oxo-1,3-oxazol-3-yl]phenyl]-1-pyridiniomethyl]-3-
cephem-4-carboxylate



1.0 g of dihydrochloride of Reference Example 1 was used as a starting material and 0.1 g of maleic anhydride was used as an acylating reagent. 10 mg of the title compound as hydrochloride salt was obtained by the same procedure in Example 1.

NMR(400MHz,DMSO-d6):

5 9.85(1H,br), 9.40~9.43(1H,d,J=6.3Hz), 8.37~8.40(2H,d,J=6.3Hz), 8.28(1H,m),
7.92~7.98(1H,m), 7.72~7.76(1H,m), 7.57~7.60(1H,m),
6.28~6.32(1H,d,J=12.3Hz), 6.17~6.21(1H,d,J=12.3Hz), 5.65~5.68(2H,m),
5.07~5.20(2H,m), 4.80(1H,m), 4.22(2H,m), 4.21(1H,m), 3.84(1H,m),
3.10~3.60(1H,ABq), 3.54(2H,m), 1.85(3H,s)

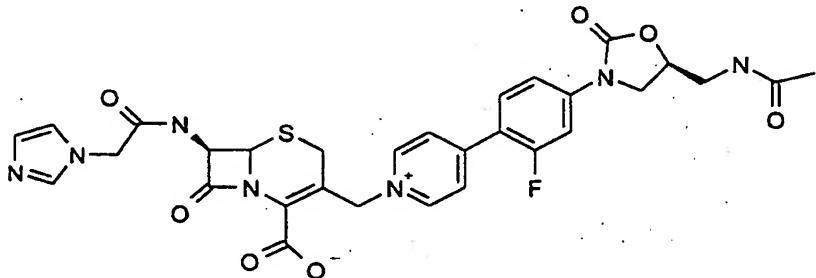
10

Example 10

Preparation of 7 β -[((1H)-1-imidazolyl)-carboxamido]-3-[4-[2-fluoro-4-[5-[(S)-methylcarboxamidomethyl]-2-oxo-1,3-oxazol-3-yl]phenyl]-1-pyridiniomethyl]-3-cephem-4-carboxylate

15

20



25 1.0 g of dihydrochloride salt of the title compound in the Reference Example 1 was used as a starting material and 0.22 g of 1H-1-imidazolylacetic acid hydrochloride of the title compound in the Reference Example 4 was used as an acylating reagent. 5 mg of the title compound as sulfate salt was obtained.

NMR(400MHz,DMSO-d6):

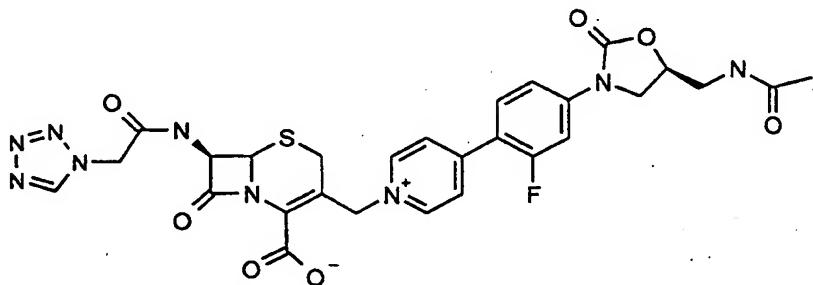
30 9.45(1H,d), 9.20(1H,d), 8.38(2H,m), 8.25(1H,t), 7.95(1H,dd), 7.73(1H,dd),
7.58(2H,m), 7.08(1H,s), 6.88(1H,s), 5.66(2H,m), 5.15(1H,d), 5.05(1H,m),
4.73~4.84(3H,m), 4.21(1H,t), 3.83(1H,dd), 3.44(2H,m), 1.84(3H,s)

Example 11

Preparation of 7β -[((1*H*)-1-tetrazolyl)-acetamido]-3-[4-[2-fluoro-4-[5-[(*S*)-methylcarboxamido-methyl]-2-oxo-1,3-oxazol-3-yl]phenyl]-1-pyridiniomethyl]-3-cephem-4-carboxylate

5

10

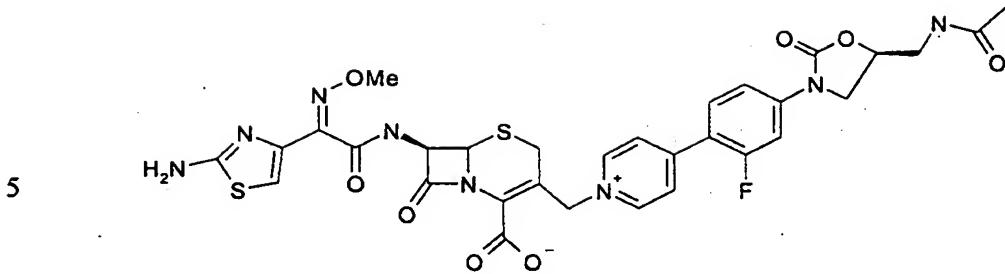


0.5 g of dihydrochloride salt of the title compound in the Reference Example 1 was dissolved in 15 ml of dichloromethane and 2.5 ml of methanol and the solution was cooled to 5°C. The cold solution was mixed with 0.37 ml of triethylamine and the mixture was stirred for 10 minutes. 0.2 g of tetrazoleacetic acid was dissolved in 5 ml of dichloromethane and the solution was cooled to -30°C. The cold solution was reacted with 0.22 ml of triethylamine and 0.2 ml of pivaloylchloride for 1 hour and was stirred at 25°C for 1 hour. This acylating reagent was dropwise added for 10 minutes and the solution was stirred for 1 hour. After the reaction was completed, the solvent was concentrated. The residue was dissolved in 50% ethanol and was purified as described in the Example 1 to obtain 30 mg of the title compound.

NMR(400MHz,DMSO-d6):
 9.30~9.47(3H,m), 9.37(1H,s), 8.38(2H,d), 8.27(1H,t), 7.95(1H,t), 7.77(1H,dd),
 7.58(2H,dd), 5.16~5.67(2H,ABq,J=13.7Hz), 5.62(1H,dd),
 5.30~5.38(2H,ABq,J=16.8Hz), 5.05(1H,d), 4.85(1H,m), 4.22(3H,m), 3.83(1H,t),
 3.44(2H,m), 3.15~3.57(2H,ABq,J=17.1Hz), 1.84(3H,s)

Example 12

Preparation of 7β -[(*Z*)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[4-[2-fluoro-4-[5-[(*S*)-methylcarboxamidoethyl]-2-oxo-1,3-oxazol-3-yl]phenyl]-1-pyridiniomethyl]-3-cephem-4-carboxylate



10 500 mg of 7β -[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-acetoxyethyl-3-cephem-4-carboxylic acid was dissolved in 10 ml of anhydrous dichloromethane under nitrogen. 0.8 ml of N-methyl-N-(trimethylsilyl)trifluoroacetamid (MSTFA) was added and the solution was stirred for 1.5 hour. After the silylation was completed, the solution was cooled to 5°C and was reacted with 0.5 ml of iodotrimethylsilane at 20°C for 30 minutes. The solution was concentrated under reduced pressure and the residue was reacted with 10 ml of acetonitrile and 1 ml of tetrahydrofuran at 5°C for 5 minutes. The prepared silylated pyridine derivative was added to the solution at 5°C and the solution was stirred at 25°C for 3 hours. This silylated pyridine derivative was prepared as follows. (S)-N-[[3-[3-fluor-4-(4-pyridyl)phenyl]-2-oxo-5-oxazolidinyl]-methyl]acetamide was used as a pyridine derivative and was synthesized according to the known method (WO 93/19103). 400 mg of the pyridine derivative was added to 10 ml of acetonitrile and the resulting solution was reacted with 1.0 ml of MSTFA at 25°C for 2 hours to produce a silylated pyridine derivative. The formed solid by adding 1.0 ml of methanol and 5 ml of acetonitrile to the solution was filtered. After the solid was dissolved in an aqueous 30% ethanol, the pH of the resulting solution was adjusted to 6.5 with saturated sodium bicarbonate and was concentrated under reduced pressure. The residue was chromatographed over silica gel using a mixed solvent of acetonitrile and water (4:1), concentrated under reduced pressure, and lyophilized to obtain 100 mg of the title compound.

15 mp: 178°C to 183°C (decomposition).

20

25

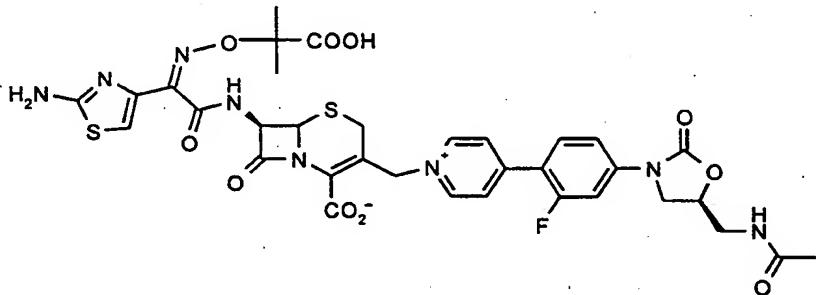
30 IR(cm^{-1}): 3411, 1760, 1617,
 NMR(400MHz,DMSO-d6):

9.60(1H,d,J=8.2Hz), 9.07~9.09(2H,m), 8.40~8.41(2H,m), 8.26~8.28(1H,m),
 7.93~7.98(1H,m), 7.57~7.76(2H,m), 7.18(2H,s), 6.72(1H,s), 5.87~5.89(1H,dd),
 5.36~5.62(1H,ABq), 5.18~5.20(1H,d), 4.74~4.83(1H,m), 4.22~4.25(1H,m),
 3.82~3.87(1H,m), 3.80(3H,s), 3.40~3.50(2H,m), 3.36~3.62(2H,ABq),
 5 1.84(3H,s)

Example 13

Preparation of 7 β -[(Z)-2-(2-aminothiazol-4-yl)-2-(1-carboxy-1-methyl-ethoxyimino)acetamido]-3-[4-[2-fluoro-4-[5-[(S)-methylcarboxamidomethyl]-2-oxo-1,3-oxazol-3-yl]phenyl]-1-pyridiniomethyl]-3-cephem-4-carboxylate

15



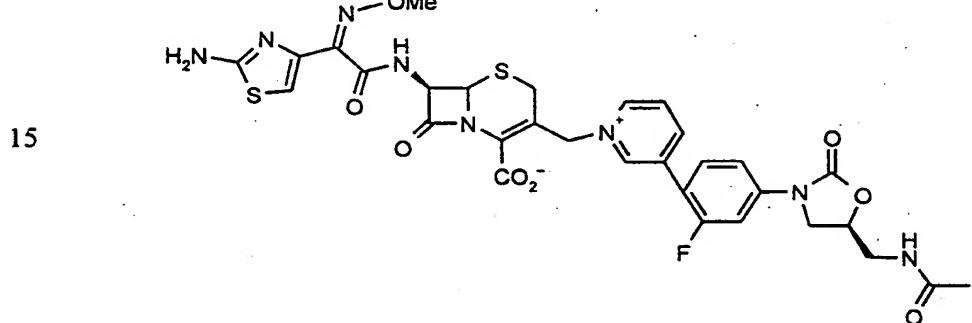
530 mg of 7 β -[(Z)-2-(2-aminothiazol-4-yl)-2-(1-carboxy-1-methyl-1-ethoxyimino)acetamido]-3-acetoxymethyl-3-cephem-4-carboxylic acid was dissolved in 10 ml of anhydrous dichloromethane under nitrogen. After the same procedure as the Example 12 was carried out by using 1.3 ml of MSTFA and 0.5 ml of TMSI, the reaction mixture was concentrated under reduced pressure. The concentrate was reacted with 10 ml of acetonitrile and 1 ml of tetrahydrofuran for 5 minutes. The solution was reacted at 25°C for 3 hours with the silylated pyridine derivatives obtained by silylating 400 mg of (S)-N-[[3-[3-fluoro-4-(4-pyridyl)phenyl]-2-oxo-5-oxazolylidinyl]-methyl]acetamide with MSTFA in 10 ml of acetonitrile. The solution was deprotected by adding 1 ml of methanol, filtered and purified to obtain 120 mg of the title compound.

mp: 174°C to 177°C (decomposition)
 20 IR(cm⁻¹): 3433, 1760, 1617, 1467, 1151
 25 NMR(DMSO-d₆):

9.42~9.45(1H,d,J=8.3Hz), 9.03~9.04(2H,m), 8.42~8.43(2H,m),
 8.23~8.24(1H,m), 7.94~7.96(1H,m), 7.59~7.77(2H,m), 7.25(2H,s), 6.70(1H,s),
 5.95~5.96(1H,dd), 5.45~5.63(2H,ABq), 5.23~5.24(1H,d), 4.78~4.82(1H,m),
 4.22~4.26(1H,m), 3.82~3.88(1H,m), 3.40~3.52(2H,m), 3.30~3.62(2H,q),
 5 1.83(3H,s), 1.41~1.43(6H,d)

Example 14

Preparation of 7 β -[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[3-[2-fluoro-4-[5-[(S)-methylcarboxamidomethyl]-2-oxo-1,3-oxazol-3-yl]phenyl]-1-pyridinio
 10 methyl]-3-cephem-4-carboxylate



20 500 mg of 7 β -[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-acetoxymethyl-3-cephem-4-carboxylic acid was dissolved in 10 ml of anhydrous dichloromethane under nitrogen. After the same procedure as Example 12 was carried out by using 0.8 ml of MSTFA and 0.5 ml of TMSI, the reaction mixture was concentrated under reduced pressure. The concentrate was reacted with 10 ml of acetonitrile and 1 ml of tetrahydrofuran for 5 minutes. The prepared silylated pyridine derivative was added to the solution at 5°C and the solution was stirred at 25°C for 3 hours. This silylated pyridine derivative was prepared as follows. (S)-N-[[3-[3-fluoro-4-(3-pyridyl)phenyl]-2-oxo-5-oxazolidinyl]-methyl]acetamide was used as a pyridine derivative and was synthesized according to the known method (WO 93/09103). 400 mg of the pyridine derivative was added to 10 ml of acetonitrile and the resulting solution was reacted with 1.0 ml of MSTFA at 25°C for 2 hours to produce the silylated pyridine

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derivative. The formed solid by adding 1.0 ml of methanol and 5 ml of acetonitrile to the solution was filtered, and purified to obtain 130 mg of the title compound.

mp: 183°C to 186°C (decomposition)

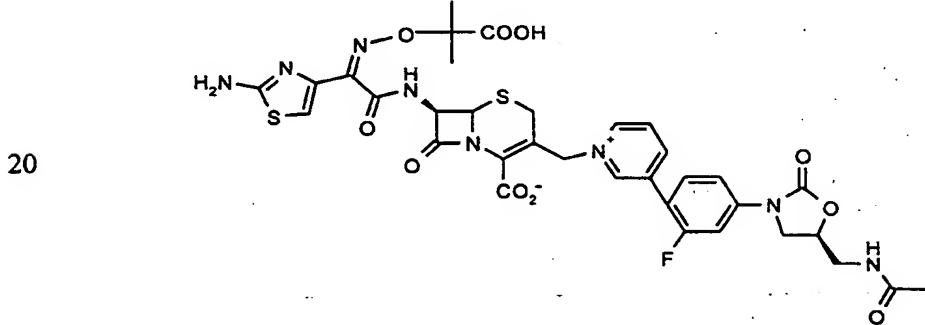
IR(cm⁻¹): 3416, 1760, 1627, 1540, 1040

5 NMR(DMSO-d₆):

9.60(1H,d,J=8.0Hz), 9.37(1H,s), 9.01~9.04(1H,m), 8.86~8.89(1H,m),
 8.25~8.31(2H,m), 7.73~7.84(2H,m), 7.56~7.58(1H,m), 7.19(2H,s), 6.71(1H,s),
 5.91~5.94(1H,dd), 5.20~5.21(1H,d), 5.62~5.70(2H,ABq), 4.77~4.82(1H,m),
 4.18~4.22(1H,m), 3.81~3.83(1H,m), 3.80(3H,s), 3.40~3.53(2H,m),
 10 3.30~3.63(2H,q), 1.84(3H,s)

Example 15

Preparation of 7β-[(Z)-2-(2-aminothiazol-4-yl)-2-(1-carboxy-1-methyl-1-ethoxyimino)acetamido]-3-[3-[2-fluoro-4-[5-[(S)-methylcarboxamidomethyl]-2-oxo-1,3-oxazol-3-yl]phenyl]-1-pyridinio methyl]-3-cephem-4-carboxylate



25 530 mg of 7β-[(Z)-2-(2-aminothiazol-4-yl)-2-(1-carboxy-1-methyl-1-ethoxyimino)acetamido]-3-acetoxymethyl-3-cephem-4-carboxylic acid was dissolved in 10 ml of anhydrous dichloromethane under nitrogen. After the same procedure as Example 12 was carried out by using 1.3 ml of MSTFA and 0.5 ml of TMSI, the reaction solution was concentrated under reduced pressure. The concentrate was reacted with 10 ml of acetonitrile and 1 ml of tetrahydrofuran for 5 minutes. The solution was reacted at 30 25°C for 3 hours with the silylated pyridine derivatives obtained by silylating 400 mg of (S)-N-[[3-[3-fluoro-4-(3-pyridyl)phenyl]-2-oxo-5-oxazolylidinyl]-methyl]acetamide with

MSTFA in 10 ml of acetonitrile. The solution was deprotected by adding 1 ml of methanol, filtered and purified to obtain 100 mg of the title compound.

mp: 175°C to 177°C (decomposition)

IR(cm⁻¹): 3433, 1760, 1617, 1467, 1151

5 NMR(DMSO-d6):

9.40~9.44(2H,m), 9.06~9.08(1H,m), 8.84~8.86(1H,m), 8.25~8.30(2H,m),
7.72~7.83(2H,m), 7.55~7.57(1H,m), 7.2(2H,s), 6.69(1H,s), 5.94~5.98(1H,dd),
5.20~5.22(1H,d), 5.60~5.66(2H,ABq), 4.78~4.83(1H,m), 4.16~4.20(1H,m),
3.81~4.84(1H,m), 3.4~3.51(2H,m), 1.84(3H,s), 1.37~1.40(6H,d)

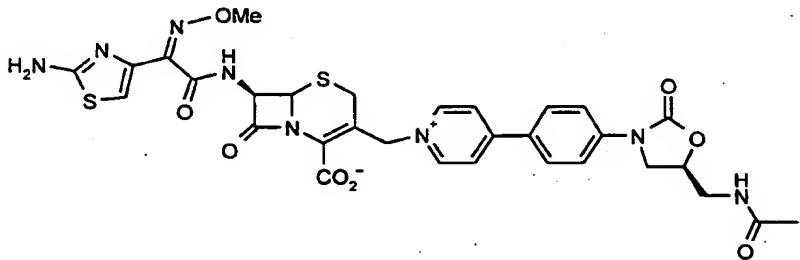
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Example 16

Preparation of 7β-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[4-[4-[5-[(S)-methyl-carboxamidomethyl]-2-oxo-1,3-oxazol-3-yl]phenyl]-1-pyridiniomethyl]-3-cephem-4-carboxylate

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500 mg of 7β-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-acetoxyethyl-3-cephem-4-carboxylic acid was dissolved in 10 ml of anhydrous dichloromethane under nitrogen. After the same procedure as the Example 12 was carried out by using 0.8 ml of MSTFA and 0.5 ml of TMSI, the reaction mixture was concentrated under reduced pressure. The concentrate was reacted with 10 ml of acetonitrile and 1 ml of tetrahydrofuran for 5 minutes. The preprepared silylated pyridine derivative was added to the solution at 5°C and the solution was stirred at 25°C for 3 hours. This silylated pyridine derivative was prepared as follows. (S)-N-[[3-[4-(4-pyridyl)phenyl]-2-oxo-5-oxazolidinyl]-methyl]acetamide was used as a pyridine derivative and was synthesized according to the known method (USP 5,254,577). 380 mg of the pyridine derivative was added to 10 ml of acetonitrile and the resulting solution

was reacted with 1.0 ml of MSTFA at 25°C for 2 hours to produce the silylated pyridine derivative. The silylated pyridine derivative was added and the solution was stirred at 25°C for 3 hours. The formed solid was filtered by adding 1.0 ml of methanol and 5 ml of acetonitrile to the solution, and purified to obtain 150 mg of the title compound. mp:

5 196°C to 198°C (decomposition)

IR(cm⁻¹): 3415, 1791, 1750, 1617,

NMR(DMSO-d6):

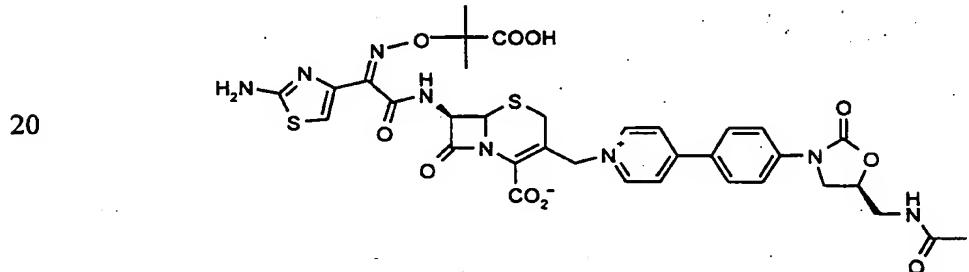
9.60(1H,d,J=7.9Hz), 8.78~8.96(2H,d), 8.54~8.56(2H,d), 8.24~8.26(1H,m),
8.16~8.19(2H,m), 7.80~7.82(2H,m), 7.25(2H,s), 6.73(1H,s), 5.87~5.89(1H,dd),

10 5.22(1H,d), 5.41~5.57(2H,ABq), 4.77~4.84(1H,m), 4.23~4.26(1H,m),

3.82~3.85(1H,m), 3.81(3H,s), 3.40~3.50(2H,m), 3.35~3.65(2H,q), 1.83(3H,s)

Example 17

Preparation of 7β-[(Z)-2-(2-aminothiazol-4-yl)-2-(1-carboxy-1-methyl-1-ethoxyimino)acetamido]-3-[4-[5-[(S)-methylcarboxamidomethyl]-2-oxo-1,3-oxazol-3-yl]phenyl]-1-pyridiniomethyl]-3-cephem-4-carboxylate



25 530 mg of 7β-[(Z)-2-(2-aminothiazol-4-yl)-2-(1-carboxy-1-methyl-1-ethoxyimino)acetamido]-3-acetoxymethyl-3-cephem-4-carboxylic acid was dissolved in 10 ml of anhydrous dichloromethane under nitrogen. After the same procedure as Example 12 was carried out by using 1.3 ml of MSTFA and 0.5 ml of TMSI, the reaction mixture was concentrated under reduced pressure. The concentrate was reacted with 10 ml of acetonitrile and 1 ml of tetrahydrofuran for 5 minutes. The solution was reacted at 25°C for 3 hours with the silylated pyridine derivatives obtained by silylating 380 mg of (S)-N-[[3-[4-(4-pyridyl)phenyl]-2-oxo-5-oxazolylidinyl]-methyl]acetamide with MSTFA

in 10 ml of acetonitrile. The solution was deprotected by adding 1 ml of methanol, filtered and purified to obtain 120 mg of the title compound.

mp: 175°C to 177°C (decomposition)

IR(cm-1): 3433, 1760, 1617, 1467, 1151

5 NMR(DMSO-d6):

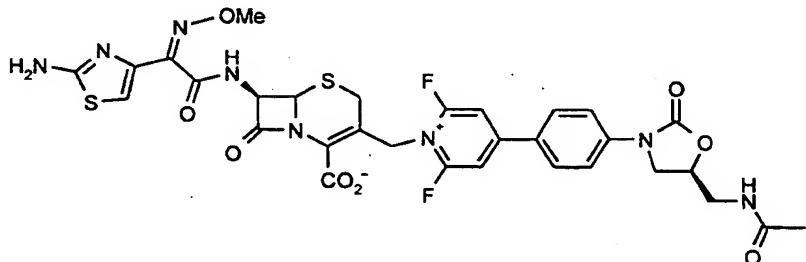
9.43~9.46(1H,d), 8.98~9.00(2H,d), 8.54~8.56(2H,d), 8.24~8.27(1H,m),
 8.16~8.18(2H,d), 7.89~7.91(2H,d), 7.28(2H,s), 6.70(1H,s), 5.90~5.95(1H,dd),
 5.22~5.23(1H,d), 5.45~5.61(2H,ABq), 4.76~4.82(1H,m), 4.18~4.24(1H,m),
 3.79~3.84(1H,m), 3.40~3.49(2H,m), 3.30~3.64(2H,q), 1.83(3H,s),
 10 1.38~1.40(6H,d)

Example 18

Preparation of 7β-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[4-[2,6-difluoro-4-[5-[(S)-methylcarboxamidomethyl]-2-oxo-1,3-oxazol-3-yl]phenyl]-1-

15 pyridiniomethyl]-3-cephem-4-carboxylate

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500 mg of 7β-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-acetoxyethyl-3-cephem-4-carboxylic acid was dissolved in 10 ml of anhydrous dichloromethane under nitrogen. After the same procedure as Example 12 was carried out by using 0.8 ml of MSTFA and 0.5 ml of TMSI, the reaction mixture was concentrated under reduced pressure. The concentrate was reacted with 10 ml of acetonitrile and 1 ml of tetrahydrofuran for 5 minutes. The preprepared silylated pyridine derivative was added to the solution at 5°C and the solution was stirred at 25°C for 3 hours. This silylated pyridine derivative was prepared as follows. (S)-N-[[3-[3,5-difluoro-4-(4-pyridyl)phenyl]-2-oxo-5-oxazolidinyl]-methyl]acetamide was used as a pyridine derivative and was

synthesized according to the known method (WO 93/09103). 420 mg of the pyridine derivative was added to 10 ml of acetonitrile and the resulting solution was reacted with 1.0 ml of MSTFA at 25°C for 2 hours to produce the silylated pyridine derivative. The formed solid by adding 1.0 ml of methanol and 5 ml of acetonitrile to the solution was 5 filtered, and purified to obtain 10 mg of the title compound.

mp: 175°C to 177°C (decomposition)

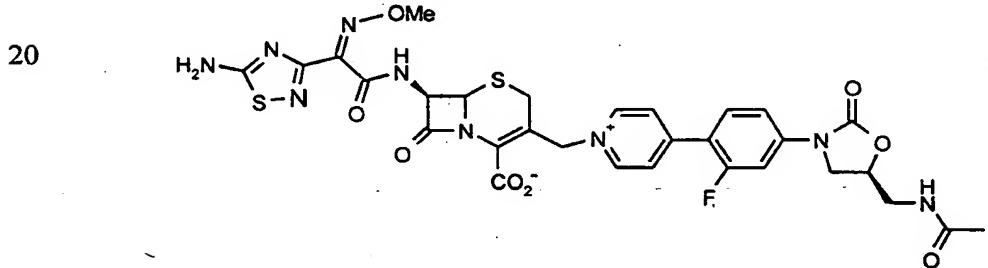
IR(cm⁻¹): 3412, 1760, 1615,

NMR(DMSO-d6):

9.60(1H,d), 9.08~9.10(2H,d), 8.37~8.39(2H,d), 8.23~8.37(1H,m),
 10 7.58~7.61(1H,d), 7.50~7.53(1H,d), 6.74(1H,s), 5.87~5.89(1H,dd),
 5.52~5.64(1H,ABq), 5.18~5.21(1H,d), 4.82~4.97(1H,m), 4.21~4.26(1H,m),
 3.82~3.87(1H,m), 3.80(3H,s), 3.41~3.51(2H,m), 3.30~3.62(2H,q), 1.85(3H,s)

Example 19

15 Preparation of 7β-[(Z)-2-(5-amino-1,2,4-thiazol-3-yl)-2-methoxyiminoacetamido]-3-[4-[2-fluoro-4-[5-[(S)-methylcarboxamidomethyl]-2-oxo-1,3-oxazol-3-yl]phenyl]-1-pyridiniomethyl]-3-cephem-4-carboxylate.



25

500 mg of 7β-[(Z)-2-(5-amino-1,2,4-thiazol-3-yl)-2-methoxyiminoacetamido]-3-acetoxymethyl-3-cephem-4-carboxylic acid [THE JOURNAL OF ANTIBIOTICS: Vol.XXXVI, No.8 p1020-1033(1983), Vol.XXXVII, No.5 p557-571(1984)] was dissolved in 10 ml of anhydrous dichloromethane under nitrogen. 0.8 ml of MSTFA was 30 added and the solution was stirred for 1.5 hour. After the silylation was completed, the solution was cooled to 5°C and was reacted with 0.5 ml of TMSI at 20°C for 30 minutes.

The solution was concentrated under reduced pressure and the residue was reacted with 10 ml of acetonitrile and 1 ml of tetrahydrofuran at 5°C for 5 minutes. The solution was reacted at 25°C for 3 hours with the silylated pyridine derivatives obtained by reacting 400 mg of (S)-N-[[3-[3-fluoro-4-(4-pyridyl)phenyl]-2-oxo-5-oxazolidinyl]-methyl]acetamide with 1.0 ml of MSTFA in 10 ml of acetonitrile. The formed solid by adding a mixed solvent of 1.0 ml of methanol and 5 ml of acetonitrile to the solution was filtered. The solid was dissolved in an aqueous 30% ethanol and the pH of the solution was adjusted to 7.0 with saturated sodium bicarbonate. The pH of the solution was then adjusted to 2.0 with 4N sulfuric acid and ethanol was added to the solution to obtain 100 mg of the title compound as sulfate salt.

10 mp: 165°C or more (decomposition)

IR(cm⁻¹): 3416, 1757

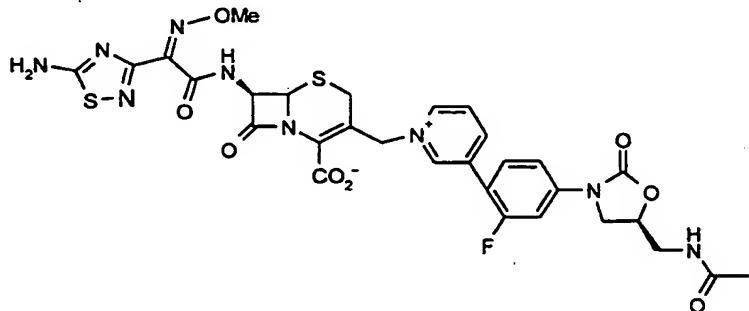
NMR(DMSO-d₆):

15 9.58(1H,d,J=8.3Hz), 9.10(2H,d), 8.44(2H,d), 8.26(1H,m), 7.94~7.97(1H,m),
7.74~7.77(2H,m), 7.59~7.61(1H,m), 5.82~5.90(1H,dd),
5.18~5.20(1H,d,J=4.9Hz), 5.44~5.62(2H,ABq,J=4.5Hz), 4.74~4.83(1H,m),
4.22~4.25(1H,m), 3.80~3.87(1H,m), 3.88(3H,s), 3.40~3.50(2H,m),
2.9~3.6(2H,m), 1.84(3H,s)

20 Example 20

Preparation of 7β-[(Z)-2-(5-amino-1,2,4-thiadiazol-3-yl)-2-methoxyiminoacetamido]-3-[3-[2-fluoro-4-[5-[(S)-methylcarboxamidomethyl]-2-oxo-1,3-oxazol-3-yl]phenyl]-1-pyridiniomethyl]-3-cephem-4-carboxylate

25



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500 mg of 7β -[(Z)-2-(5-amino-1,2,4-thiadiazol-3-yl)-2-methoxyiminoacetamido]-3-acetoxyethyl-3-cephem-4-carboxylic acid was dissolved in 10 ml of anhydrous dichloromethane under nitrogen. The solution was reacted with 0.8 ml of MSTFA and 0.5 ml of TMSI by the same method as the Example 19. The solution was concentrated under reduced pressure and the concentrate was reacted with 10 ml of acetonitrile and 1 ml of tetrahydrofuran for 5 minutes. The solution was reacted at 25°C for 3 hours with the silylated pyridine derivatives obtained by reacting 400 mg of (S)-N-[[3-[3-fluoro-4-(3-pyridyl)phenyl]-2-oxo-5-oxazolidinyl]-methyl]acetamide with 1.0 ml of MSTFA in 10 ml of acetonitrile. The resulting solid by adding a mixed solvent of 1.0 ml of methanol and 5 ml of acetonitrile to the solution was filtered. The solid was dissolved in an aqueous 30% ethanol and the pH of the solution was adjusted to 7.0 with saturated sodium bicarbonate. The pH of the solution was then adjusted to 2.0 with 4N sulfuric acid and ethanol was added to the solution to obtain 110 mg of the title compound as sulfate salt.

10 mp: 145°C or more (decomposition)

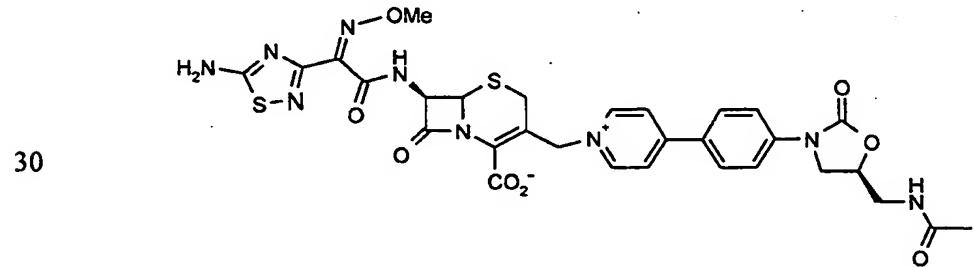
15 IR(cm⁻¹): 3418, 1760

NMR(DMSO-d₆):

20 9.50~9.56(2H,m), 9.20(1H,s), 8.80~8.85(1H,m), 8.25~8.32(2H,m),
 7.70~7.85(2H,m), 7.50~7.60(1H,m), 5.82~5.89(1H,dd), 5.20(1H,d),
 5.50~5.70(2H,ABq), 4.76~4.82(1H,m), 4.18~4.23(1H,m), 3.80~3.85(1H,m),
 3.86(3H,s), 3.40~3.50(2H,m), 1.85(3H,s)

Example 21

Preparation of 7β -[(Z)-2-(5-amino-1,2,4-thiadiazol-3-yl)-2-methoxyiminoacetamido]-3-[4-[4-[5-[(S)-methylcarboxamidomethyl]-2-oxo-1,3-oxazol-3-yl]phenyl]-1-pyridiniomethyl]-3-cephem-4-carboxylate



500 mg of 7β -[(Z)-2-(5-amino-1,2,4-thiadiazol-3-yl)-2-methoxyiminoacetamido]-3-acetoxymethyl-3-cephem-4-carboxylic acid was dissolved in 10 ml of anhydrous dichloromethane under nitrogen. The solution was reacted with 0.8 ml of MSTFA and 0.5 ml of TMSI by the same method as the Example 19. The solution was concentrated under reduced pressure and the concentrate was reacted with 10 ml of acetonitrile and 1 ml of tetrahydrofuran for 5 minutes. The solution was reacted at 25°C for 3 hours with the silylated pyridine derivatives obtained by reacting 380 mg of (S)-N-[[3-[4-(4-pyridyl)phenyl]-2-oxo-5-oxazolidinyl]-methyl]acetamide with 1.0 ml of MSTFA in 10 ml of acetonitrile. The resulting solid by adding a mixed solvent of 1.0 ml of methanol and 5 ml of acetonitrile to the solution was filtered. The solid was dissolved in an aqueous 30% ethanol and the pH of the solution was adjusted to 7.0 with saturated sodium bicarbonate. The pH of the solution was then adjusted to 2.0 with 4N sulfuric acid and ethanol was added to the solution to obtain 150 mg of the title compound as sulfate salt. mp: 170°C or more (decomposition)

15 IR(cm⁻¹): 3415, 1760

NMR(DMSO-d₆):

9.58(1H,d), 8.80~9.00(2H,d), 8.54~8.58(2H,d), 8.24~8.26(1H,m),
8.16~8.20(2H,m), 7.80~7.84(2H,m), 5.85~5.90(1H,dd), 5.18~5.20(1H,d),
5.42~5.60(2H,ABq), 4.78~4.83(1H,m), 4.22~4.25(1H,m), 3.80~3.85(1H,m),
3.87(3H,s), 3.40~3.50(2H,m), 1.84(3H,s)

Antibacterial Activity Test

25 The *in vitro* antibacterial activities of the compounds prepared by Examples 1 through 21 were tested as described in Chemotherapy, 29(1), 76, 1981. Vancomycin and cefotaxime were used as control. Their MICs (Minimum Inhibition Concentration: μ g/ml) by agar dilution were measured and the result is indicated in Table 2 below.

Table 2

	A	B	C	D	E	F	G	H	I	
5	1	0.50	1.00	1.00	0.25	1.00	0.06	32.0	4.00	>32.0
	2	1.00	1.00	1.00	0.25	0.50	0.06	32.0	2.00	>32.0
	3	1.00	1.00	1.00	0.25	1.00	0.06	>32.0	2.00	>32.0
	4	1.00	2.00	2.00	0.50	2.00	0.06	32.0	4.00	>32.0
	5	1.00	2.00	2.00	0.50	2.00	0.06	>32.0	8.00	>32.0
	6	2.00	1.00	1.00	0.50	1.00	0.25	>32.0	8.00	>32.0
10	7	2.00	2.00	2.00	0.50	1.00	0.25	>32.0	4.00	>32.0
	8	2.00	2.00	2.00	1.00	2.00	0.50	>32.0	32.0	>32.0
	9	8.00	4.00	4.00	2.00	8.00	1.00	>32.0	16.0	>32.0
	10	1.00	1.00	1.00	0.25	1.00	0.06	>32.0	4.00	>32.0
	11	1.00	2.00	2.00	0.25	4.00	0.06	8.00	4.00	>32.0
	12	1.00	2.00	1.00	0.25	1.00	0.06	0.12	0.06	1.00
15	13	2.00	2.00	2.00	1.00	2.00	0.12	0.25	0.12	0.50
	14	2.00	2.00	2.00	0.50	2.00	0.06	0.25	0.25	2.00
	15	2.00	2.00	2.00	0.50	2.00	0.06	0.12	0.25	1.00
	16	2.00	4.00	4.00	0.50	2.00	0.06	0.25	0.12	0.25
	17	2.00	4.00	4.00	1.00	2.00	0.12	0.50	0.25	1.00
	18	2.00	2.00	2.00	0.50	2.00	0.50	2.00	0.25	0.50
20	19	1.00	2.00	2.00	1.00	2.00	0.06	0.12	0.06	2.00
	20	2.00	2.00	2.00	0.50	2.00	0.06	0.12	0.25	0.50
	21	2.00	4.00	4.00	1.00	4.00	0.06	0.12	0.25	2.00
	C1	0.25	0.25	0.25	0.25	0.25	0.06	32	0.25	32
	C2	2.00	32	128	1.00	128	0.06	0.06	0.06	0.06
	C3	1.00	1.00	1.00	1.00	2.00	0.25	128	128	128

A: *Staphylococcus aureus* ATCC29213B: MRSA C5100 (Methicillin resistant *Staphylococcus aureus*)

C: CRSA C6043 (Ciprofloxacin resistant *Staphylococcus aureus*)
D: *Staphylococcus epidermidis* ATCC12228
E: *Enterococcus faecalis* ATCC29212
F: *Streptococcus pyogenes* ATCC8668
5 G: *Escherichia coli* ATCC10536
H: *Klebsiella pneumoniae* ATCC10031
I: *Proteus mirabilis* ATCC25933
C1: (S)-N-[[3-[3-fluoro-4-(4-pyridyl)phenyl]-2-oxo-5-oxazolidinyl]-methyl]acetamide
C2: Cefotaxime
10 C3: Vancomycin

As can be seen from the above Table 2, the compounds of the formula I according to the present invention are broadly active against Gram-positive and Gram-negative bacteria and have the pharmacological advantages of vancomycin and cefotaxime.
15 Especially, the compounds of the formula I are advantageous in that they are effective against cephem antibiotics-resistant bacteria such as MRSA and CRSA.

Toxicity Test

20 The single dose toxicity of the compounds of the present invention was evaluated in ICR mice by intravenous administration. The compounds of Examples 1, 2 and 13 along with an equivalent of sodium bicarbonate were dissolved in saline and the resulting solutions were intravenously administered. LD₅₀ of each test compound was measured to be 1,500 mg/kg of weight.

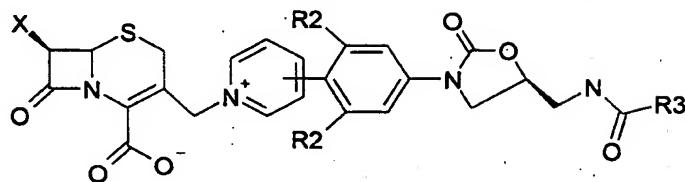
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WHAT IS CLAIMED IS:

1. A compound of the formula I:

5



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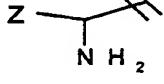
or pharmaceutically acceptable salts or hydrates thereof wherein

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X is i) amine or protected amine, ii) $\text{Y}-\text{C}(=\text{O})-\text{N}(\text{R})-\text{X}$ in which Y is i) hydrogen, ii) C₁-C₆ lower alkyl optionally substituted with at least one selected from the group consisting of chlorine, fluorine, cyano, nitro, hydroxy, amino, C₁-C₄ alkylamino, C₁-C₄ dialkylamino, hydroxylamino, C₁-C₄ alkoxyamino, C₁-C₄ alkoxyimino, C₁-C₄ alkoxy, C₁-C₄ acyloxy, C₁-C₄ alkylsulfonyl, C₁-C₄ alkylsulfonyl, C₁-C₄ alkylsulfinyl, C₁-C₄ alkylaminosulfonyl, and carboxylic acid and inorganic cation salt thereof, iii) C₂-C₆ alkenyl optionally substituted with at least one selected from the group consisting of chlorine, fluorine, cyano, nitro, hydroxy, amino, C₁-C₄ alkylamino, C₁-C₄ dialkylamino, hydroxylamino, C₁-C₄ alkoxyamino, C₁-C₄ alkoxyimino, C₁-C₄ alkoxy, C₁-C₄ acyloxy, C₁-C₄ alkylsulfonyl, C₁-C₄ alkylsulfonyl, C₁-C₄ alkylsulfinyl, C₁-C₄ alkylaminosulfonyl, and carboxylic acid and inorganic cation salt thereof, iv) C₂-C₆ alkynyl optionally substituted with at least one selected from the group consisting of chlorine, fluorine, cyano, nitro, hydroxy, amino, C₁-C₄ alkylamino, C₁-C₄ dialkylamino, hydroxylamino, C₁-C₄ alkoxyamino, C₁-C₄ alkoxyimino, C₁-C₄ alkoxy, C₁-C₄ alkylsulfonyl, C₁-C₄ alkylsulfonyl, C₁-C₄ alkylsulfinyl, C₁-C₄ alkylaminosulfonyl, and carboxylic acid and inorganic cation salt thereof, v) phenyl optionally substituted with at least one selected from the group consisting of chlorine, fluorine, cyano, nitro, hydroxy, amino, C₁-C₄ alkylamino, C₁-C₄ dialkylamino, hydroxylamino, C₁-C₄ alkoxyamino, C₁-C₄ alkoxyimino, C₁-C₄ alkoxy, C₁-C₄ acyloxy, C₁-C₄ alkylsulfonyl, C₁-C₄ alkylsulfonyl, C₁-C₄ alkylsulfinyl, C₁-C₄ alkylaminosulfonyl, and carboxylic acid and inorganic cation salt thereof, vi) R₄-(CH₂)_n-,

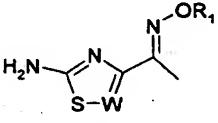
in which n is an integer of 0 to 3, and R4 is 2-thiophenyl, 2-furyl, 2-pyrolyl, 4-thiazolyl, 1,2,4-thiadiazol-3-yl, 2-oxazolyl, or 5- or 6- membered heterocyclic compound having from 1 to 4 atoms of O, S and N which are substituted with at least one selected from the group consisting of chlorine, fluorine, hydroxy, amino, C₁-C₄ alkyl, C₁-C₄ acylamino, C₁-

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C₄ alkylsulfonylamino, C₁-C₄ alkoxy, and C₁-C₄ acyloxy, vii)  in which Z is hydrogen, or C₁-C₆ lower alkyl, C₁-C₆ alkenyl, C₂-C₆ alkynyl, phenyl or heterocyclic compound optionally substituted with at least one selected from the group consisting of chlorine, fluorine, cyano, nitro, hydroxy, amino, C₁-C₄ alkylamino, C₁-C₄ dialkylamino, 10 hydroxylamino, C₁-C₄ alkoxyamino, C₁-C₄ alkoxyimino, C₁-C₄ alkoxy, C₁-C₄ acyloxy, C₁-C₄ alkylsulfonyl, C₁-C₄ alkylsulfenyl, C₁-C₄ alkylsulfinyl, C₁-C₄ alkylaminosulfonyl, and carboxylic acid and inorganic cation salt thereof, and carbon having optical activity can

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be optically pure (-), (+) or racemic forms, viii)  in which W is CH or N, R₁ is hydrogen, or lower alkyl optionally substituted with carboxylic acid or inorganic cation salt thereof or protected carboxylic acid, and the alkoxyimino is a syn isomer;

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R2 is hydrogen, fluorine, chlorine or methoxy and can be same or different;

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R3 is hydrogen, or lower alkyl optionally substituted with carboxy or inorganic cation salt thereof, amino or alkoxy; and

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provided that in the compounds of the formula I the phenyloxazolidinone is substituted at 3 or 4 positions of pyridine.

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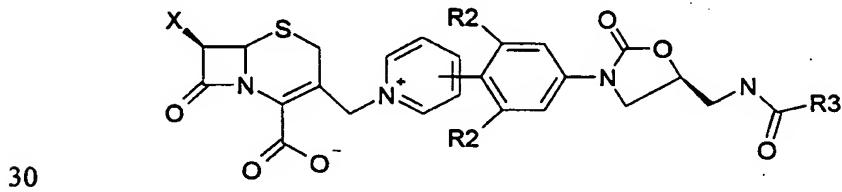
2. The compound according to claim 1 in which R2 is independently hydrogen or fluorine.

3. The compound according to claim 1 in which R3 is hydrogen, methyl, difluoromethyl, trichloromethyl, hydroxymethyl or methoxy.

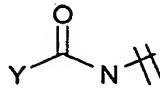
4. The compound according to claim 1 which is
7 β -acetamido-3-[4-[2-fluoro-4-[5-[(S)-methylcarboxamidomethyl]-2-oxo-1,3-oxazol-3-yl]phenyl]-1-pyridiniomethyl]-3-cephem-4-carboxylate;
7 β -[2-hydroxy-acetamido]-3-[4-[2-fluoro-4-[5-[(S)-methylcarboxamidomethyl]-2-oxo-1,3-oxazol-3-yl]phenyl]-1-pyridiniomethyl]-3-cephem-4-carboxylate;
5 7 β -[2-hydroxy-2-methyl-acetamido]-3-[4-[2-fluoro-4-[5-[(S)-methylcarboxamidomethyl]-2-oxo-1,3-oxazol-3-yl]phenyl]-1-pyridiniomethyl]-3-cephem-4-carboxylate;
7 β -[2-cyclopropyl-acetamido]-3-[4-[2-fluoro-4-[5-[(S)-methylcarboxamidomethyl]-2-oxo-1,3-oxazol-3-yl]phenyl]-1-pyridiniomethyl]-3-cephem-4-carboxylate;
10 7 β -[2-methyl-acetamido]-3-[4-[2-fluoro-4-[5-[(S)-methylcarboxamidomethyl]-2-oxo-1,3-oxazol-3-yl]phenyl]-1-pyridiniomethyl]-3-cephem-4-carboxylate;
7 β -[2-amino-acetamido]-3-[4-[2-fluoro-4-[5-[(S)-methylcarboxamidomethyl]-2-oxo-1,3-oxazol-3-yl]phenyl]-1-pyridiniomethyl]-3-cephem-4-carboxylate;
15 7 β -[2-(N,N'-dimethylamino)-3-[4-[2-fluoro-4-[5-[(S)-methylcarboxamidomethyl]-2-oxo-1,3-oxazol-3-yl]phenyl]-1-pyridiniomethyl]-3-cephem-4-carboxylate;
7 β -[perhydro-2-pyrolyl-carboxamido]-3-[4-[2-fluoro-4-[5-[(S)-methylcarboxamidomethyl]-2-oxo-1,3-oxazol-3-yl]phenyl]-1-pyridiniomethyl]-3-cephem-4-carboxylate;
7 β -[2-carboxy-(Z)-1-ethenyl-carboxamido]-3-[4-[2-fluoro-4-[5-[(S)-methylcarboxamidomethyl]-2-oxo-1,3-oxazol-3-yl]phenyl]-1-pyridiniomethyl]-3-cephem-4-
20 carboxylate;
7 β -[((1H)-1-imidazolyl)-carboxamido]-3-[4-[2-fluoro-4-[5-[(S)-methylcarboxamidomethyl]-2-oxo-1,3-oxazol-3-yl]phenyl]-1-pyridiniomethyl]-3-cephem-4-carboxylate;
7 β -[((1H)-1-tetrazolyl)-acetamido]-3-[4-[2-fluoro-4-[5-[(S)-methylcarboxamido-methyl]-2-oxo-1,3-oxazol-3-yl]phenyl]-1-pyridiniomethyl]-3-cephem-4-carboxylate;
25 7 β -[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[4-[2-fluoro-4-[5-[(S)-methylcarboxamidomethyl]-2-oxo-1,3-oxazol-3-yl]phenyl]-1-pyridiniomethyl]-3-cephem-4-carboxylate;
7 β -[(Z)-2-(2-aminothiazol-4-yl)-2-(1-carboxy-1-methyl-ethoxyimino)acetamido]-3-[4-[2-fluoro-4-[5-[(S)-methylcarboxamidomethyl]-2-oxo-1,3-oxazol-3-yl]phenyl]-1-
30 pyridiniomethyl]-3-cephem-4-carboxylate;
7 β -[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[3-[2-fluoro-4-[5-[(S)-

5-methylcarboxamidomethyl]-2-oxo-1,3-oxazol-3-yl]phenyl]-1-pyridiniomethyl]-3-
cephem-4-carboxylate;
 7 β -[(Z)-2-(2-aminothiazol-4-yl)-2-(1-carboxy-1-methyl-1-ethoxyimino)acetamido]-3-[3-
[2-fluoro-4-[5-[(S)-methylcarboxamidomethyl]-2-oxo-1,3-oxazol-3-yl]phenyl]-1-
5 pyridiniomethyl]-3-cephem-4-carboxylate;
 7 β -[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[4-[4-[5-[(S)-methyl-
carboxamidomethyl]-2-oxo-1,3-oxazol-3-yl]phenyl]-1-pyridiniomethyl]-3-cephem-4-
10 carboxylate;
 7 β -[(Z)-2-(2-aminothiazol-4-yl)-2-(1-carboxy-1-methyl-1-ethoxyimino)acetamido]-3-[4-
[4-[5-[(S)-methylcarboxamidomethyl]-2-oxo-1,3-oxazol-3-yl]phenyl]-1-
15 pyridiniomethyl]-3-cephem-4-carboxylate;
 7 β -[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[4-[2,6-difluoro-4-[5-[(S)-
methylcarboxamidomethyl]-2-oxo-1,3-oxazol-3-yl]phenyl]-1-pyridiniomethyl]-3-
20 cephem-4-carboxylate;
 7 β -[(Z)-2-(5-amino-1,2,4-thiazol-3-yl)-2-methoxyiminoacetamido]-3-[4-[2-fluoro-4-[5-
[(S)-methylcarboxamidomethyl]-2-oxo-1,3-oxazol-3-yl]phenyl]-1-pyridiniomethyl]-3-
25 cephem-4-carboxylate;
 7 β -[(Z)-2-(5-amino-1,2,4-thiadiazol-3-yl)-2-methoxyiminoacetamido]-3-[3-[2-fluoro-4-
[5-[(S)-methylcarboxamidomethyl]-2-oxo-1,3-oxazol-3-yl]phenyl]-1-pyridiniomethyl]-3-
30 cephem-4-carboxylate; or
 7 β -[(Z)-2-(5-amino-1,2,4-thiadiazol-3-yl)-2-methoxyiminoacetamido]-3-[4-[4-[5-[(S)-
methylcarboxamidomethyl]-2-oxo-1,3-oxazol-3-yl]phenyl]-1-pyridiniomethyl]-3-
cephem-4-carboxylate.

25 5. A process for producing a compound of the formula I:



or pharmaceutically acceptable salts or hydrates thereof wherein



X is i) amine or protected amine; ii) in which Y is i) hydrogen, ii) C₁-C₆

5 lower alkyl optionally substituted with at least one selected from the group consisting of chlorine, fluorine, cyano, nitro, hydroxy, amino, C₁-C₄ alkylamino, C₁-C₄ dialkylamino, hydroxylamino, C₁-C₄ alkoxyamino, C₁-C₄ alkoxyimino, C₁-C₄ alkoxy, C₁-C₄ acyloxy, C₁-C₄ alkylsulfonyl, C₁-C₄ alkylsulfenyl, C₁-C₄ alkylsulfinyl, C₁-C₄ alkylaminosulfonyl, and carboxylic acid and inorganic cation salt thereof, iii) C₂-C₆ alkenyl optionally substituted with at least one selected from the group consisting of chlorine, fluorine, cyano, nitro, hydroxy, amino, C₁-C₄ alkylamino, C₁-C₄ dialkylamino, hydroxylamino, C₁-C₄ alkoxyamino, C₁-C₄ alkoxyimino, C₁-C₄ alkoxy, C₁-C₄ acyloxy, C₁-C₄ alkylsulfonyl, C₁-C₄ alkylsulfenyl, C₁-C₄ alkylsulfinyl, C₁-C₄ alkylaminosulfonyl, and carboxylic acid and inorganic cation salt thereof, iv) C₂-C₆ alkynyl optionally substituted with at least one selected from the group consisting of chlorine, fluorine, cyano, nitro, hydroxy, amino, C₁-C₄ alkylamino, C₁-C₄ dialkylamino, hydroxylamino, C₁-C₄ alkoxyamino, C₁-C₄ alkoxyimino, C₁-C₄ alkoxy, C₁-C₄ acyloxy, C₁-C₄ alkylsulfonyl, C₁-C₄ alkylsulfenyl, C₁-C₄ alkylsulfinyl, C₁-C₄ alkylaminosulfonyl, and carboxylic acid and inorganic cation salt thereof, v) phenyl optionally substituted with at least one selected from the group consisting of chlorine, fluorine, cyano, nitro, hydroxy, amino, C₁-C₄ alkylamino, C₁-C₄ dialkylamino, hydroxylamino, C₁-C₄ alkoxyamino, C₁-C₄ alkoxyimino, C₁-C₄ alkoxy, C₁-C₄ acyloxy, C₁-C₄ alkylsulfonyl, C₁-C₄ alkylsulfenyl, C₁-C₄ alkylsulfinyl, C₁-C₄ alkylaminosulfonyl, and carboxylic acid and inorganic cation salt thereof, vi) R4-(CH₂)_n-, in which n is an integer of 0 to 3, and R4 is 2-thiophenyl, 2-furyl, 2-pyrolyl, 4-thiazolyl, 1,2,4-thiadiazol-3-yl, 2-oxazolyl, or 5- or 6- membered heterocyclic compound having from 1 to 4 atoms of O, S and N which are substituted with at least one selected from the group consisting of chlorine, fluorine, hydroxy, amino, C₁-C₄ alkyl, C₁-C₄ acylamino, C₁-C₄ alkylsulfonylamino, C₁-C₄ alkoxy, and C₁-C₄ acyloxy, vii) Z-NH₂ in which

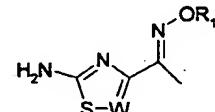
20 Z is hydrogen, or C₁-C₆ lower alkyl, C₁-C₆ alkenyl, C₂-C₆ alkynyl, phenyl or heterocyclic compound optionally substituted with at least one selected from the group consisting of

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chlorine, fluorine, cyano, nitro, hydroxy, amino, C_1 - C_4 alkylamino, C_1 - C_4 dialkylamino, hydroxylamino, C_1 - C_4 alkoxyamino, C_1 - C_4 alkoxyimino, C_1 - C_4 alkoxy, C_1 - C_4 acyloxy, C_1 - C_4 alkylsulfonyl, C_1 - C_4 alkylsulfenyl, C_1 - C_4 alkylsulfinyl, C_1 - C_4 alkylaminosulfonyl, and carboxylic acid and inorganic cation salt thereof, and carbon having optical activity can

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be optically pure (-), (+) or racemic forms, viii) in which W is CH or N, R1 is hydrogen, or lower alkyl optionally substituted with carboxylic acid or inorganic cation salt thereof or protected carboxylic acid, and the alkoxyimino is a syn isomer;

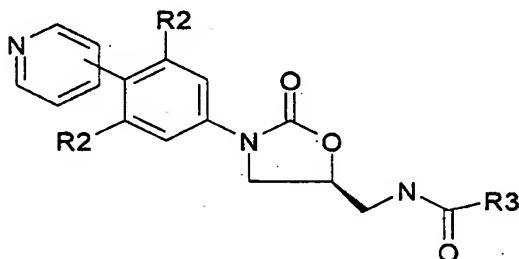
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R2 is hydrogen, fluorine, chlorine or methoxy and can be same or different;

R3 is hydrogen, or lower alkyl optionally substituted with carboxy or inorganic cation salt thereof, amino or alkoxy; and

provided that in the compounds of the formula I the phenyloxazolidinone is substituted at 3 or 4 positions of pyridine, which comprises reacting a compound of the formula II:

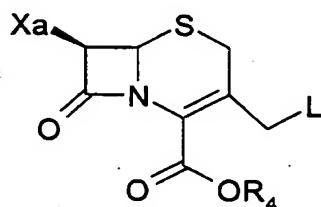
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wherein R2 and R3 are same as defined above, with a compound of the formula III:

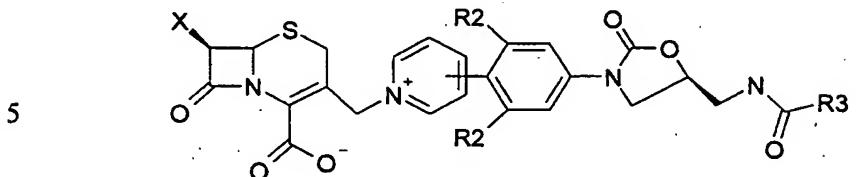
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wherein Xa is the same as X defined above, except for amine and protected amine, R4 is hydrogen or carboxylic acid-protecting group, and L is halogen atom or acetoxy, to produce the compound of the formula I.

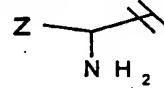
6. A process for producing a compound of the formula I:



or pharmaceutically acceptable salts or hydrates thereof wherein

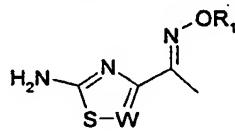
10 X is i) amine or protected amine, ii) $\text{Y} \begin{array}{c} \text{O} \\ \parallel \\ \text{C} \\ \backslash \\ \text{N} \end{array} \text{X}$ in which Y is i) hydrogen, ii) C₁-C₆ lower alkyl optionally substituted with at least one selected from the group consisting of chlorine, fluorine, cyano, nitro, hydroxy, amino, C₁-C₄ alkylamino, C₁-C₄ dialkylamino, hydroxylamino, C₁-C₄ alkoxyamino, C₁-C₄ alkoxyimino, C₁-C₄ alkoxy, C₁-C₄ acyloxy, C₁-C₄ alkylsulfonyl, C₁-C₄ alkylsulfenyl, C₁-C₄ alkylsulfinyl, C₁-C₄ alkylaminosulfonyl, and carboxylic acid and inorganic cation salt thereof, iii) C₂-C₆ alkenyl optionally substituted with at least one selected from the group consisting of chlorine, fluorine, cyano, nitro, hydroxy, amino, C₁-C₄ alkylamino, C₁-C₄ dialkylamino, hydroxylamino, C₁-C₄ alkoxyamino, C₁-C₄ alkoxyimino, C₁-C₄ alkoxy, C₁-C₄ acyloxy, C₁-C₄ alkylsulfonyl, C₁-C₄ alkylsulfenyl, C₁-C₄ alkylsulfinyl, C₁-C₄ alkylaminosulfonyl, and carboxylic acid and inorganic cation salt thereof, iv) C₂-C₆ alkynyl optionally substituted with at least one selected from the group consisting of chlorine, fluorine, cyano, nitro, hydroxy, amino, C₁-C₄ alkylamino, C₁-C₄ dialkylamino, hydroxylamino, C₁-C₄ alkoxyamino, C₁-C₄ alkoxyimino, C₁-C₄ alkoxy, C₁-C₄ acyloxy, C₁-C₄ alkylsulfonyl, C₁-C₄ alkylsulfenyl, C₁-C₄ alkylsulfinyl, C₁-C₄ alkylaminosulfonyl, and carboxylic acid and inorganic cation salt thereof, v) phenyl optionally substituted with at least one selected from the group consisting of chlorine, fluorine, cyano, nitro, hydroxy, amino, C₁-C₄ alkylamino, C₁-C₄ dialkylamino, hydroxylamino, C₁-C₄ alkoxyamino, C₁-C₄ alkoxyimino, C₁-C₄ alkoxy, C₁-C₄ acyloxy, C₁-C₄ alkylsulfonyl, C₁-C₄ alkylsulfenyl, C₁-C₄ alkylsulfinyl, C₁-C₄ alkylaminosulfonyl, and carboxylic acid and inorganic cation salt thereof, vi) R4-(CH₂)_n-, in which n is an integer of 0 to 3, and R4 is 2-thiophenyl, 2-furyl, 2-pyrol, 4-thiazolyl, 1,2,4-thiadiazol-3-yl, 2-oxazolyl, or 5- or 6- membered heterocyclic compound having

from 1 to 4 atoms of O, S and N which are substituted with at least one selected from the group consisting of chlorine, fluorine, hydroxy, amino, C_1 - C_4 alkyl, C_1 - C_4 acylamino, C_1 -



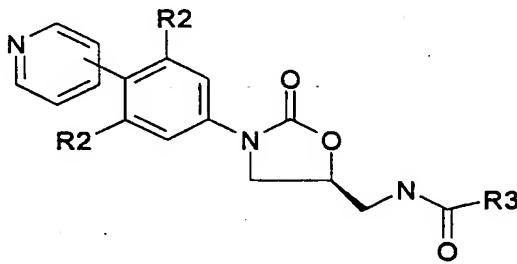
C_4 alkylsulfonylamino, C_1 - C_4 alkoxy, and C_1 - C_4 acyloxy, vii)

5 is hydrogen, or C_1 - C_6 lower alkyl, C_1 - C_6 alkenyl, C_2 - C_6 alkynyl, phenyl or heterocyclic compound optionally substituted with at least one selected from the group consisting of chlorine, fluorine, cyano, nitro, hydroxy, amino, C_1 - C_4 alkylamino, C_1 - C_4 dialkylamino, hydroxylamino, C_1 - C_4 alkoxyamino, C_1 - C_4 alkoxyimino, C_1 - C_4 alkoxy, C_1 - C_4 acyloxy, C_1 - C_4 alkylsulfonyl, C_1 - C_4 alkylsulfenyl, C_1 - C_4 alkylsulfinyl, C_1 - C_4 alkylaminosulfonyl, and 10 carboxylic acid and inorganic cation salt thereof, and carbon having optical activity can



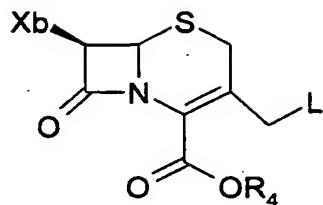
be optically pure (-), (+) or racemic forms, viii) in which W is CH or N, R1 is hydrogen, or lower alkyl optionally substituted with carboxylic acid or inorganic cation salt thereof or protected carboxylic acid, and the alkoxyimino is a syn isomer;

15 R2 is hydrogen, fluorine, chlorine or methoxy and can be same or different; R3 is hydrogen, or lower alkyl optionally substituted with carboxy or inorganic cation salt thereof, amino or alkoxy; and provided that in the compounds of the formula I the phenyloxazolidinone is substituted 20 at 3 or 4 positions of pyridine, which comprises reacting a compound of the formula II:



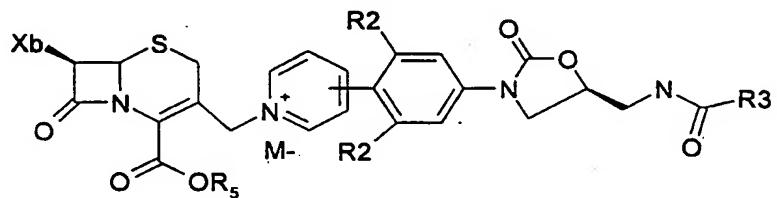
wherein R2 and R3 are same as defined above, with a compound of the formula IV:

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wherein Xb is amine or protected amine, R₄ is hydrogen or carboxylic acid-protecting group, and L is the same as defined above, to produce a compound of the formula V:

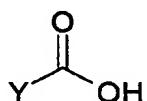
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wherein R₂ and R₃ are the same as defined above, Xb is amine or protected amine, R₅ is hydrogen or carboxylic acid-protecting group, M⁺ is anionic halogen, or sulfate, acetate, benzenesulfonate or citrate anions, with the compounds of the formula VI:

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wherein Y is the same as defined above, to produce the compound of the formula.

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7. An antibacterial composition comprising antibacterially effective amount of the compound according to claim 1 and pharmaceutically acceptable carrier.

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/KR 98/00463

A. CLASSIFICATION OF SUBJECT MATTER

IPC⁶: C 07 D 501/24; A 61 K 31/545

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC⁶: C 07 D 501/24

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

DARC

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 93/09 103 A1 (THE UPJOHN COMPANY) 13 May 1993 (13.05.93), claim 1 (cited in the application).	1-7
A	US 5 254 577 A (CARLSON et al.) 19 October 1993 (19.10.93), claims 1,16,31 (cited in the application).	1-7

Further documents are listed in the continuation of Box C.

See patent family annex.

* Special categories of cited documents:

„A“ document defining the general state of the art which is not considered to be of particular relevance

„E“ earlier application or patent but published on or after the international filing date

„L“ document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

„O“ document referring to an oral disclosure, use, exhibition or other means

„P“ document published prior to the international filing date but later than the priority date claimed

„T“ later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

„X“ document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

„Y“ document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

„&“ document member of the same patent family

Date of the actual completion of the international search

08 March 1999 (08.03.99)

Date of mailing of the international search report

17 March 1999 (17.03.99)

Name and mailing address of the ISA/AT

Austrian Patent Office

Kohlmarkt 8-10; A-1014 Vienna

Facsimile No. 1/53424/535

Authorized officer

Brus

Telephone No. 1/53424/519

INTERNATIONAL SEARCH REPORT

International application No.
PCT/KR 98/00463

WO 93/09 103 A1

The present invention discloses novel substituted aryl- and heteroarylphenoxyazolidinones which are useful as antibacterial agents. More specifically, the substituted aryl- and heteroarylphenyl oxazolidinones of the invention are characterized by oxazolidinones having an aryl or heteroaryl group at the *p*-position of the 3-phenyl ring and additional substitutions at the *m*-position(s) of the 3-phenyl ring. A compound representative of this new class of oxazolidinones is (\pm)-5-(acetamidomethyl)-3-[4-(3-pyridyl)-3,5-difluorophenyl]-2-oxazolidinone.

US 5 254 577 A

Novel aminomethyloxooxazolidinyl arylbenzene derivatives, wherein the aryl includes the phenyl, substituted phenyl, pyridyl, and substituted pyridyl groups, such as (1)-N-{3-[4-(4'-pyridyl)=phenyl]-2-oxooxazolidin-5-ylmethyl}-acetamide, possess useful antibacterial activity.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/KR 98/00463

Im Recherchenbericht angeführtes Patentdokument Patent document cited in search report Document de brevet cité dans le rapport de recherche	Datum der Veröffentlichung Publication date Date de publication	Mitglied(er) der Patentfamilie Patent family member(s) Membre(s) de la famille de brevets	Datum der Veröffentlichung Publication date Date de publication
WO A1 9309103	13-05-93	AT E 146783 AU A1 26898/92 AU B2 667198 DE CO 69216251 DE T2 69216251 DK T3 610265 EP A1 610265 EP B1 610265 GR T3 3022340 JP T2 7500603 US A 5565571 US A 55654428 US A 55654435 US A 5756732 US A 5801246	15-01-97 07-06-93 14-03-96 06-02-97 15-05-97 09-06-97 17-08-94 27-12-96 30-04-97 19-01-95 15-10-96 05-08-97 05-08-97 26-05-98 01-09-98
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